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ACTION OF PREDNISONE IN INSULIN-RESISTANT DIABETES

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The term "insulin resistant" has generally been applied to those diabetics whose daily insulin requirement exceeds 200 units. Such diabetics are relatively rare; Kleeberg, Diengott, and Gottfried (1956) found only some 50 instances in the literature. The purpose of this paper is to report the results of immunological and other studies on an additional 13 cases, 6 of them treated with prednisone.

The factors responsible for insulin resistance are not known with certainty, but include certain hormones and other substances in the serum, some of which have the properties of antibody and others which are of a different nature. The ability of serum from insulin-resistant diabetic patients to protect animals from the hypoglycaemic action of insulin was demonstrated in rabbits by Glen and Eaton (1938) and in mice by Lowell (1942), who developed the mouse-convulsion test. Marsh and Haugaard (1952), using the rat-diaphragm technique described by Stadie *et al.* (1949), reported insulin inhibition by sera from normal patients, from mild diabetics, and, to a much greater degree, from three severely insulin-resistant diabetics. Using a similar diaphragm technique, Field and Stetten (1956) were able to demonstrate the presence of an insulin antagonist in the alpha-globulin fraction of diabetics with severe ketosis, and Vallance-Owen, Dennes, and Campbell (1958) in the albumin fraction of plasma from uncontrolled insulin-requiring diabetics and also from normal subjects.

For various reasons insulin has been regarded as poorly antigenic, but successful immunization in rabbits has been reported by Wasserman, Broh-Kahn, and Mirsky (1940), and also by Moloney and Coval (1955), who produced immune serum in guinea-pigs, using cattle and pig insulin as antigens. Berson *et al.* (1956) have shown that, in almost all human subjects receiving exogenous insulin, antibodies capable of binding insulin *in vivo* and *in vitro* soon appear. It would seem, therefore, that the difference between insulin resistance and non-resistance in insulin-treated patients may be essentially a quantitative one. In this connexion the work of Berson and Yalow (1957) suggests that the total insulin-binding capacity of sera from non-resistant treated subjects is of the order of 10 units per litre of plasma, whereas binding capacities of as much as 500 units per litre of plasma were found in sera from insulin-resistant patients.

In 1938 Glen and Eaton reported the case of a severely insulin-resistant girl whose insulin requirement fell after the administration of oestrogen, but, apart from this isolated instance, until recently no effective method of treatment has been described. Fortunately, perseverance with large doses of insulin has in most cases been followed by a spontaneous fall in insulin requirement to a much lower but still usually fairly high figure.

Collens and Banowitch (1955) reported the case of a severely insulin-resistant diabetic whose daily insulin requirement subsequently fell from 1,000 to 200 units when given cortisone in large doses. Colwell and Weiger (1956), using corticotrophin, obtained an even more spectacular reduction of insulin requirement from 11,400 to 100 units in a case of haemochromatosis. Similar responses to corticotrophin have been reported by Kleeberg, Diengott, and Gottfried (1956) and by Gitelson and Wislicki (1956).

Methods

In the present study anti-insulin factors were demonstrated by one or more of the following three methods—the mouse-convulsion test, the glucose uptake of the rat hemi-diaphragm, and passive cutaneous anaphylaxis in the guinea-pig. The first two tests have been described by Lowell (1942) and Field and Rigby (1959) respectively; they have been used to demonstrate the presence of anti-insulin substances without distinction between insulin antagonists and insulin antibodies; while the third test, hitherto never used in this connexion, has been adapted by one of us (A.C.C.) to detect insulin antibodies.

Mouse-convulsion Test

In this test samples of plasma from an insulin-resistant diabetic, an insulin-sensitive diabetic, and a normal control are examined. Dilutions of insulin are made in each plasma and injected into fasted mice housed at 34° C. The same concentration of insulin in acid saline is injected into control groups of mice, and hypoglycaemic convulsions are recorded over a period of one and a quarter hours.

Glucose Uptake of Rat Hemi-diaphragm (R.D. Test)

This test depends on the fact that a rat hemi-diaphragm exposed to insulin and serum will utilize about 40% more glucose than a control hemi-diaphragm exposed only to serum. A significant decrease in this insulin effect in the presence of the test serum is

interpreted as evidence for the presence in the serum of an anti-insulin factor. A quantitative estimation of the amount of such factor or factors has been made by testing tenfold dilutions of the test serum, an example of which is shown in Table I; the titre has been expressed as the highest dilution causing a significant decrease in the insulin effect.

TABLE I.—*Rat Diaphragm Titrations on Plasma from a Resistant Diabetic and from Normal Patients*

Dilution of Plasma	Insulin Effect (Micromols Glucose Equivalent per g. Tissue (Mean ± S.E.)		
	Plasma from Case 4		Normal Plasma
	Before Treatment	After Treatment	
1:1	−0·23 ± 0·33 (3)	—	2·74 ± 0·17 (51)
1:10	0·58 ± 0·49 (3)	1·34 ± 0·57 (6)	2·41 ± 0·10 (89)
1:100	−0·02 ± 0·26 (3)	2·35 ± 0·51 (3)	2·07 ± 0·23 (15)
1:1,000	2·32 ± 0·16 (3)	—	2·16 ± 0·27 (3)

Figures in parentheses indicate number of experiments.

Passive Cutaneous Anaphylaxis in the Guinea-pig (P.C.A. Test)

This test depends upon three facts. (1) The guinea-pig is highly susceptible to anaphylaxis and can be readily sensitized to shock by passive transfer of antibody. (2) Whereas a relatively large systemic dose of the appropriate antigen is required to induce fatal anaphylactic shock, the intracutaneous injection of a very much smaller amount results in an immediate and essentially reversible skin reaction, known as cutaneous anaphylaxis, which is characterized by a transient increase in capillary permeability. Since wealing does not occur in guinea-pig skin and erythema is difficult to observe, this increased permeability is best detected when the animal has previously been injected with a suitable dye, and its extent can then be measured by the staining of the skin which results from the escape of dye from the circulation (Ramsdell, 1928). (3) A strictly localized area of sensitization can be produced by the injection of small doses of antibody into the skin. Ovary (1952) and Ovary and Bier (1953) showed that the extent of this local sensitization could be used as a very delicate measure of precipitating antibody in rabbit serum. The procedure they found most sensitive is that known as reversed P.C.A.; in this, the antiserum is injected intracutaneously, and the challenge dose of the appropriate antigen is given intravenously together with "pontamine" or Evans blue; an interval of 4 to 24 hours for skin sensitization is left between the injection of the serum and the challenge with antigen.

Brocklehurst, Humphrey, and Perry (1955), who titrated a pneumococcus polysaccharide-antipneumococcus serum system by reversed P.C.A. in the rat, noted that the diameter of the area of increased permeability, shown by dye escape, was proportional to the logarithm of the dose of antibody, and pointed out the greater precision of titration that can result from this knowledge. The same dose–lesion relationship was found by Cunliffe (1959) while titrating several different antigen–antibody systems by P.C.A. in the guinea-pig.

The reversed P.C.A. technique was used for the detection of antibody to insulin after preliminary experiments had shown that intravenous insulin resulted in well-marked anaphylactic reactions in guinea-pigs previously injected with serum from an insulin-resistant diabetic; control sera gave no reaction. That this was a specific reaction to insulin and not to other tissue antigens of the animal from which the insulin was obtained is proved by the fact that sera gave almost identical P.C.A. reactions to pig and to ox insulins; no increased permeability reactions were produced when ox or pig serum was used as antigen in place of insulin. A quantitative result was obtained by injecting a series of dilutions of the serum under test and comparing the size of the resulting P.C.A. lesions with those given by a standard serum injected into the same animals. This use of a reference serum was necessary because of the considerable variation in the reactivity of individual guinea-pigs.

Details of Technique of P.C.A. Test for Insulin Antibodies

The procedure is that of reversed P.C.A. The animals used were albino guinea-pigs weighing 350-500 g., all of which were bred from the same stock. Depilation was obtained by a short application of a barium sulphide paste to the previously clipped hair of the back and flanks (Miles and Miles, 1952). Pontamine sky blue 6 BX (G. T. Gurr) was made up in sterile saline to a 5% solution. The dose given to the animals was 6 mg./kg. body weight. Insulin (Boots), strength 320 units per ml., was used at a dosage of 160 units/kg. as the challenge antigen. The sera were stored without preservative at −20° C.; these were thawed and dilutions made in physiological saline immediately before testing.

The serum from Case 1 was kept as the reference serum and assigned the arbitrary titre of 1 in 27. Threefold dilutions of both test and reference sera were made and 0.1 ml. was injected intracutaneously at 16 random sites on the back and flanks of three or more depilated guinea-pigs. Four to 24 hours later pontamine blue was given into the femoral vein and followed immediately by insulin in a dose of 160 units/kg., also intravenously. (When human sera of relatively low titre were titrated, the 24-hour period of sensitization was found more satisfactory than shorter intervals because of non-specific permeability effects.) The animals were examined 30 minutes after the injection of insulin for evidence of increased capillary permeability at the sites where serum was injected. The diameter of the blue-stained lesions was measured and the titre recorded after comparing the lesion size of various dilutions of the unknown with the reference serum.

Results of P.C.A. Tests

The P.C.A. test has been carried out on 30 non-diabetic controls and on 72 diabetics, of whom 20 were untreated, 13 were on diet only, 26 were treated with insulin over long periods, and 13 had severe insulin resistance; the results are summarized in Table II. The

TABLE II.—*Passive Cutaneous Anaphylaxis Tests for Antibody to Insulin*

Source of Serum	No. of Sera with Titre				Total
	<1/3	1/3	1/9	1/27	
Non-diabetics (controls) ..	30				30
Diabetics:					
Untreated	20				20
Diet only	13				13
Insulin (15 years) ..	24		2		26
,, resistant ..	2	1	4	6	13

two long-standing insulin-treated diabetics who gave positive P.C.A. tests were males receiving 100 and 74 units of insulin daily respectively.

Six of the 13 insulin-resistant cases were treated with prednisone and are described below. The results obtained in the remaining seven are shown in Table III, from which it will be seen that, although in five there had been a spontaneous fall in insulin requirement, all gave a positive P.C.A. test.

TABLE III.—*Details of Seven Untreated Cases of Insulin Resistance*

Case No.	Sex and Age	Insulin Onset to Insulin-resistance	Insulin Requirement (Units/Day)		Serum Titre	
			Maximum	When Serum Tested	P.C.A	R.D.
7	M 78	6 months	1,920	112	1:27	>1:1
8	M 74	1½ ,,	780	76	1:9	1:10
9	M 64	12 years	780	200	1:1	1:1
10	F 75	12 months	570	500	1:27	1:10
11	M 66	5 ,,	272	180	1:3	1:1
12	F* 37	Not known	212	212	1:3	>1:1
13	M 68	8 months	1,008	56	1:9	N.T.

* Pregnant N.T.=Not tested

In view of the encouraging reports of the use of corticotrophin and cortisone in the treatment of severely insulin-resistant diabetics referred to above, it was decided to treat with prednisone any such cases that attended the diabetic clinic at King's College Hospital, and we were fortunate in finding five such patients within the course of a comparatively few months; to this number Dr. J. D. N. Nabarro has kindly allowed us to add a sixth (Case 4), similarly treated by him at the Middlesex Hospital.

Clinical Details of Patients Before Treatment

Case 1.—A man of 64 gave a nine-months history of diabetes with subacute onset, and had lost 4 stone (25.4 kg.) in the six months before treatment. The diabetes had been initially controlled by a diet containing 200 g. of carbohydrate and 36 units of insulin zinc suspension. He began to develop insulin resistance after he had been on insulin for about three months, and when first seen by us was taking over 1,000 units daily; he had been on as much as 2,500 units. There was no family history of diabetes. On examination the only abnormal physical findings were slight enlargement of the liver, some brown pigmentation of the skin of both forearms, and well-marked signs of diabetic neuropathy. Special investigations, which included the electrophoretic pattern of plasma proteins, urinary steroid excretion, serum iron concentration, and Co_2 combining power, were all normal. The sedimentation rate, usually raised in cases of insulin resistance, was only 9 mm. After seven weeks in hospital the diabetes was finally controlled by two daily doses of soluble insulin together amounting to 816 units (Fig. 1).

Case 2.—A man of 54 developed diabetes with subacute onset in 1950 at the age of 46. There was no family history of diabetes. The disease was controlled by a diet containing 220 g. of carbohydrate and a mixed dose of 16 units of soluble insulin with 8 units of protamine-zinc insulin. After nine months the insulin requirement began to rise, and in 1954 was 284 units. He was first admitted to the diabetic department at King's College Hospital in 1956, the positive findings then being an enlarged liver, pigmentation over shoulders and back, testicular atrophy, and marked signs of diabetic neuropathy. Liver-function tests were at or just above the upper limit of normal, and steroid excretions, serum iron, and iron-combining power were all normal. E.S.R. was 52. Insulin requirement at that time was 448 units, and was unaffected by carbutamide. In 1957 he was readmitted for treatment with prednisone. The physical signs and investigations were much as before, but liver-function tests showed improvement. There was a slight increase in gamma-globulin by electrophoresis, and the E.S.R. was 71. Tomograms of the pituitary fossa were normal. The diabetes was stabilized on 720 units (Fig. 2).

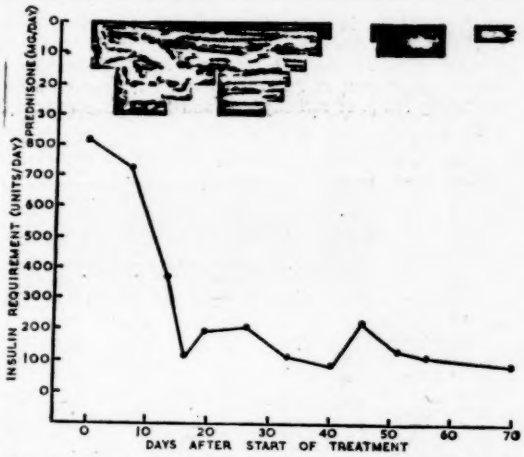

FIG. 1.—Case 1 Response to prednisone after four months of severe insulin resistance.

Case 3.—A man of 73 had had diabetes since 1938. After a brief initial period of insulin therapy, his diabetes was controlled by diet alone until March, 1958, when insulin had again to be given; good control was maintained until June. In July the insulin dosage began to mount, and when he was admitted to King's in pre-coma on July 31 it had risen to 200 units daily, his blood sugar then being 540 mg./100 ml. On examination he was anaemic, Hb 60%, and there was enlargement of the liver, spleen, and lymph nodes. Thymol turbidity was 7, but other liver-function tests were within normal limits. Total serum proteins were 5.9 g./100 ml., and electrophoresis showed a slight increase in the alpha$_2$-fraction. Other investigations were normal, but biopsy of a lymph node showed the histological picture of lymphosarcoma. The insulin was rapidly increased until stabilization was achieved on a daily dose of 1,264 units of soluble insulin (Fig. 3).

Case 4.—A man aged 73 was found to have diabetes in 1954, and responded well to diet and insulin. He was able to discontinue insulin in 1955, at which time he developed rheumatoid arthritis. In October, 1957, he was put on prednisone for a short while, but as this aggravated his diabetes and necessitated a return to insulin it was discontinued. By December, 1957, he was taking 1,400 units

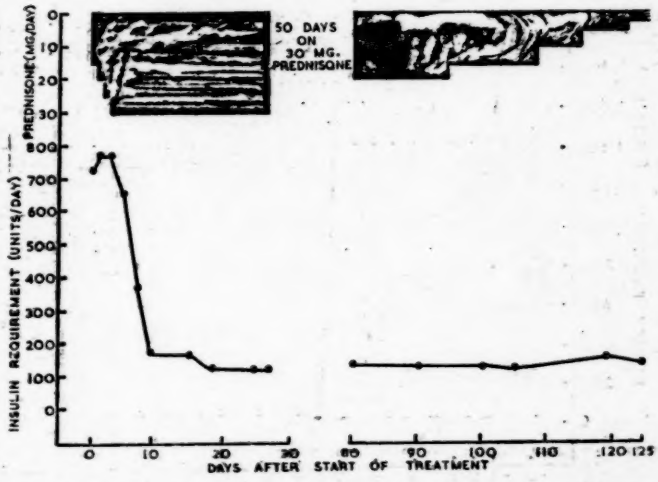

FIG. 2.—Case 2. Response to prednisone after 18 months of severe insulin resistance.

of insulin daily, in spite of which he had marked hyperglycaemia and ketonuria. He was admitted to the Middlesex Hospital under Dr. Nabarro, and after reaching a maximum insulin requirement of 2,240 units was stabilized on a diet containing 100 g. of carbohydrate and 1,440 units of insulin (Fig. 4).

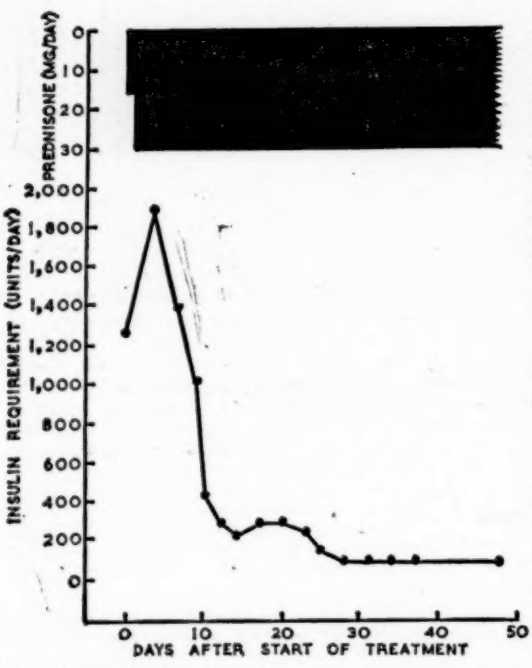

FIG. 3.—Case 3. Response to prednisone after six weeks of severe insulin resistance.

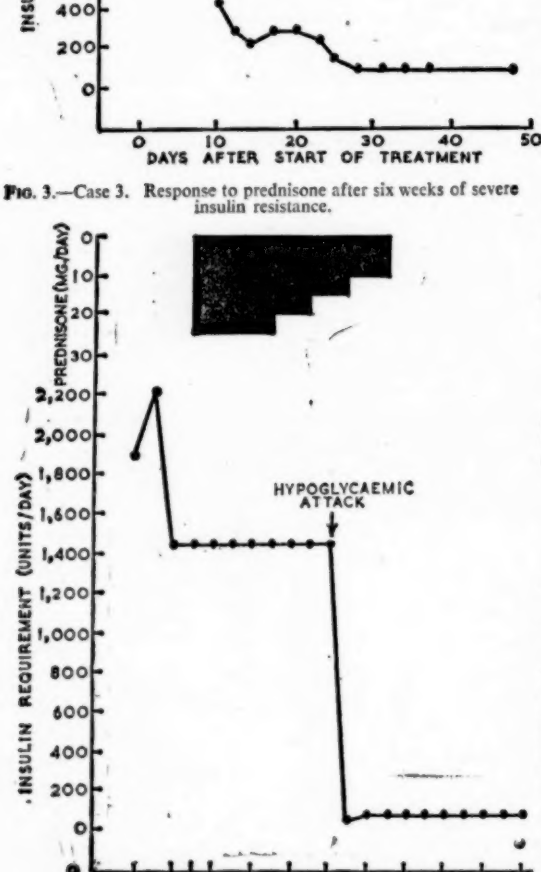

FIG. 4.—Case 4. Response to prednisone after two months of severe insulin resistance.

Case 5.—A girl of 13 developed signs of obstructive jaundice in May, 1957. She was admitted to the Mayday Hospital in June with jaundice, enlarged liver and spleen, and evidence of severe liver damage. Plasma bilirubin was 7.3 mg./100 ml., zinc sulphate flocculation 39 units, and plasma proteins 9.4 g./100 ml., with great excess of gamma-globulin. In September she developed diabetes with ketosis and a blood sugar of 398 mg./100 ml. There was no family history of diabetes. Liver biopsy showed diffuse hepatic fibrosis, more pronounced within the portal tracts. On admission to the diabetic department at King's she was slightly jaundiced; her liver was three fingerbreadths below the costal margin and the spleen just palpable. Plasma proteins were 9.0 g./100 ml., with marked increase in gamma-globulin fraction. Liver-function tests were all abnormal, and her E.S.R. was 67 mm. Urinary steroids were low, but plasma cortisol was within normal limits, as also was the serum iron concentration. The diabetes was first satisfactorily controlled on 200 g. of carbohydrate and 236 units of soluble insulin (Fig. 5).

Case 6.—A West Indian man aged 32 was first seen three weeks after the acute onset of diabetes. There was a

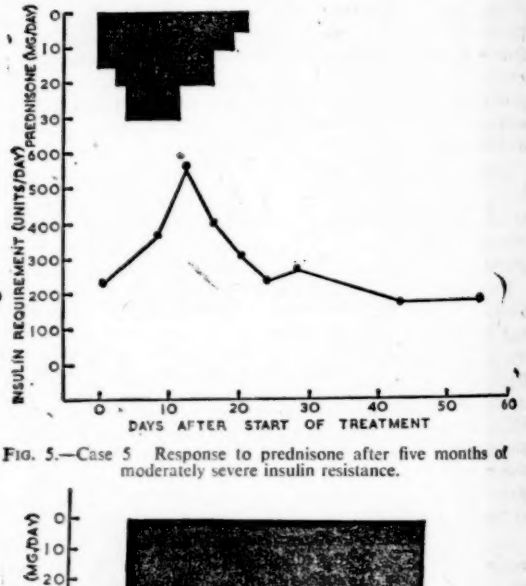

FIG. 5.—Case 5 Response to prednisone after five months of moderately severe insulin resistance.

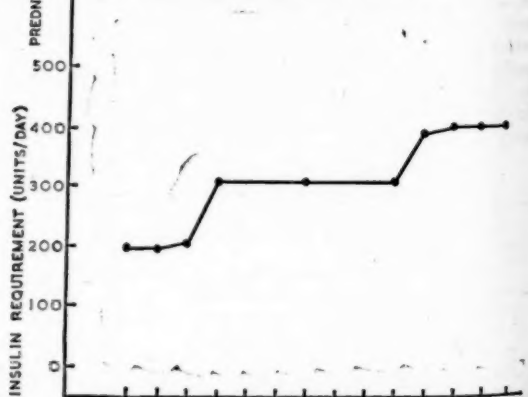

FIG. 6.—Case 6. Response to prednisone four weeks after diagnosis of diabetes.

doubtful history of mild diabetes in his father but no other family history of the disease. In addition to the classical symptoms there was a history of generalized pruritus and boils for four to five months. Physical examination was negative, and the E.S.R. 9 mm. Liver-function tests, total serum proteins, and electrophoresis were all normal, as also were 17-ketosteroid and ketogenic steroid levels. The diabetes was controlled on a diet containing 250 g. of carbohydrate and 312 units of insulin (Fig. 6); this was later reduced to 200 units.

Results of Treatment with Prednisone

The results of treatment with prednisone in respect both of insulin requirement and of P.C.A. and rat-diaphragm tests are summarized in Table IV, individual responses to prednisone being shown in Figs. 1 to 6. In Cases 1 to 4, inclusive, the P.C.A. test was positive and there was a prompt and sustained fall in insulin requirement, beginning four to seven days after the onset of treatment with prednisone. The first case was treated before it was possible to carry out any biological tests for insulin resistance, and the serological tests were made three months after the drug had been stopped. The mouse convulsion test was performed before and after treatment in Case 2 only; before prednisone the plasma from this case protected mice against the hypoglycaemic convulsive action of injected insulin, while after prednisone the action of the plasma in this respect was similar to that of plasma from an insulin-sensitive diabetic and afforded no such protection.

Prednisone treatment in Cases 2, 3, and 4 was followed by a more marked reduction in the titre of both P.C.A. and R.D. tests than was observed in Case 1, but these sera were taken either while the patients were still on prednisone or very soon after its withdrawal.

In Case 5 the administration of prednisone was followed by a steep rise in insulin requirement (400 units), and the P.C.A. test was negative both before and after treatment; the R.D. test was weakly positive at both times (Fig. 5). Case 6 was the only patient resistant to insulin from the start of treatment. In this case the P.C.A. test was negative on three occasions, but it was not possible to carry out R.D. tests. The insulin requirement rose steadily while prednisone was being given, and since its withdrawal has so far shown no sign of falling (Fig. 6).

Late Results.—Case 1 had no prednisone for eight months and his daily insulin requirement remained at about 100 units; this rose during the next three months to 176 units, and he was put back on 5 mg. of prednisone, on which he now requires 108 units. Case 2 felt unwell and developed anorexia when prednisone was withdrawn; 17 months later he was having 2 mg. of prednisone and 136 units insulin. Case 3 has been maintained on 15 mg. of cortisone because of lymphosarcoma, and his insulin requirement has remained unchanged at 80 units. Case 4, when last seen in March, 1958, needed 320 units of insulin, and was having 10 mg. of prednisone to control his arthritis. Case 5 has been maintained on 10 mg. of cortisone, as this seems to be having some beneficial effect on her liver condition; her insulin requirement is now 156 units. In Case 6 the insulin requirement six weeks after the onset of treatment was 400 units.

Discussion

The demonstration of the presence in the sera of insulin-resistant diabetics of substances capable of neutralizing the action of insulin has led to many attempts to discover their nature and aetiological significance. Evidence that some of these sera contained insulin antibodies was obtained by haemagglutination (Arquilla and Stavitsky, 1956) and less directly by the insulin-binding property of the globulin fraction (Berson *et al.*, 1956).

The results reported in this paper favour the view that insulin resistance may be produced by an excess of insulin antibodies inasmuch as prednisone has been shown to cause a rapid and dramatic fall in the insulin requirement of those cases in which it has been possible, by means of the P.C.A. test, to demonstrate the presence of antibodies; the failure of prednisone to exert this action in the two cases in which the P.C.A. test was negative is in keeping with this view, but requires confirmation. The multiplicity of action of prednisone makes it unwise to presume its site of action, but it is not possible at present in any other way to explain this action of prednisone, which normally increases insulin requirement.

From evidence already quoted it would appear that the production of insulin antibody is common in insulin-treated diabetics, but the haemagglutination studies of Moinat (1958) showed no relation between the titre and either the dose of insulin or the duration of its administration. We were unable by means of the P.C.A. test to demonstrate antibody in the sera of insulin-sensitive diabetics except in two cases receiving respectively 100 and 74 units of insulin; both gave low titres, and in one the history suggested the possibility of previous episodes of resistance. It is reasonable, therefore, to conclude that either the P.C.A. test is less sensitive than the techniques of haemagglutination and insulin-binding or that it is detecting a different type of insulin antibody.

In our cases the time interval between the onset of insulin administration and that of insulin resistance is relatively short, being 12 months or less in 12 out of 13 cases and six months or less in seven cases. Owing to the inevitable difficulty in assessing the time of onset of resistance, these figures suggest the possibility of an even closer time relationship. It may also be significant that in two cases there was a history of insulin having

TABLE IV.—*Details of Five Cases of Insulin Resistance Treated with Prednisone*

Case No.	Sex and Age	Pre-prednisone				Post-prednisone		
		Insulin Onset to Insulin-resistance in Months	Insulin Requirement Units/Day	P.C.A. Titre	R.D. Titre	Insulin Requirements	P.C.A. Titre	R.D. Titre
1	M 64	3	816	N.T.	N.T.	80	1:27	1:10
2	M 54	9	720	1:27	1:100	120	<1:3	1:1
3	M 73	4	1,264	1:27	1:10	84	<1:3	1:10
4	M 73	3*	1,440	1:27	1:100	80	<1:3	1:1
5	F 13	Nil	236	<1:3	1:1	240	<1:3	1:1
6	M 32	,,	200	<1:3	N.T.	400	<1:3	N.T.

* Insulin for short while 3 years previously. N.T. = Not tested.

been given for a short time and then restarted after a long interval of treatment by diet alone. In this connexion it is not very uncommon for manifestations of insulin allergy to be associated with a return to insulin therapy. None of our cases showed such manifestations, but the association between allergy and resistance has been noted on a number of occasions (Berne and Wallerstein, 1950). The reason why greater amounts of antibody are not formed in response to insulin treatment may possibly be related to the method of its administration; in no course of prophylactic immunization is antigen given once or more daily over long periods. The restarting of insulin might well be expected to act as a booster dose, and, on general principles, be more likely to lead to greater antibody production.

The results of the P.C.A. and R.D. tests obtained in our cases support the widely held view that there are a number of different causes of insulin resistance. It can be assumed that a serum giving a positive P.C.A. test contains insulin antibodies, whereas the R.D. test is capable of detecting several different types of antagonist. In Case 5 the P.C.A. test was negative and the R.D. test positive, but it is significant that P.C.A. antibodies have not been found when the serum contained no demonstrable antagonist. At present prednisone appears to benefit a group of insulin-resistant diabetics whose daily insulin requirement is nearer 1,000 than 200 units and in whom can be found no apparent cause for the resistance. The time interval between the start of insulin treatment and the development of resistance is usually less than a year, and often between three and six months; in our experience all such cases have had demonstrable insulin antibodies.

Summary

Thirteen cases of insulin-resistant diabetes are presented, six of which have been treated with prednisone. The anti-insulin factors have been studied, and the mouse convulsion test and glucose uptake of the rat diaphragm (R.D.) have been used to demonstrate the presence of insulin antagonists; insulin antibodies have been detected by a reversed passive cutaneous anaphylaxis (P.C.A.) technique. This P.C.A. test is described, with results obtained in normal controls and in insulin-sensitive and insulin-resistant diabetics.

Prednisone produced a dramatic fall in insulin requirement in the four cases in which the P.C.A. test was positive, but had the opposite and more usual effect in the two cases in which this test was negative. The suggestion is made that those diabetics in whom insulin resistance is associated with demonstrable insulin antibodies possess certain common clinical features.

We thank Dr. G. A. Stewart, of the Wellcome Biological Control Laboratories, for carrying out the mouse convulsion tests, Dr. Herbert Levy for allowing us access to Cases 10 and 12, and Dr. J. D. N. Nabarro for permission to publish the details of Case 4. This work was supported by a grant from the Joint Research Committee of King's College Hospital and Medical School.

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CHEMOTHERAPY OF NON-TUBERCULOUS PULMONARY INFECTIONS*

BY

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The acute and chronic non-tuberculous infections of the lung constitute an excellent subject for debate concerning the principles and practice of chemotherapy. The respiratory tract is probably subject to attack by a greater number of species of bacteria and of viruses than any other. The effects of these organisms range from trifling illnesses to disorders which are rapidly fatal. Chemotherapy can claim some of its most brilliant successes in this field, but must also admit to disastrous defeat. If the subject of chemotherapy is really so delightfully logical as our bacteriological colleagues assure us, it should be easy to lay down the principles of treatment for the patient with a pulmonary infection. Unfortunately, clinicians know that there are no simple rules for success and that diagnostic acumen and vigilant observation are demanded by each and every case.

Background for Pulmonary Infections

It is a truism that chemotherapy has transformed the prognosis for the case of ordinary pneumonia and that the mortality from pneumonia has declined dramatically. Yet it is often forgotten that the decline in mortality antedated the introduction in 1938 of the sulphonamides active against the pneumococcus. Since then the mortality from pneumonia has declined further and all age groups have shared in the benefit. Much less change has occurred in the death rate from bronchitis, which, in any case, shows some fluctuation from year to year. The actual numbers of cases of pneumonia are, of course, greatly influenced by influenza epidemics, and it is probably unwise to attribute alterations in prevalence to the effects of therapy. But a great change has undoubtedly occurred in the past twenty years in the clinical presentation of pneumonia. Lobar pneumonia is no longer seen with any frequency in hospital practice. And the situation in general practice has become complex.

Thus the pneumonias of the aged and acute illnesses in those subject to chronic disease such as bronchiectasis

*Read to a Plenary Session at the Annual Meeting of the British Medical Association, Birmingham, 1958.

and chronic bronchitis bulk largely in the total numbers of cases seen in practice. Moreover, the patients with clear-cut signs of consolidation form a minority of all those with acute chest illnesses. The College of General Practitioners (1956) reported that consolidation was found in only 12% of 1,757 cases of acute chest infection seen in general practice. Shaw and Fry (1955) found that radiological changes were often present in patients with localized rales and a severe degree of illness even though signs of consolidation were absent. Truly the diagnostic problem in general practice is now considerable. No one can be sure whether this change results from an evolution in disease perhaps related to host factors or to the effect of chemotherapy on the epidemiology of the naso-pharyngeal organisms capable of attacking the lung.

Bacterial Pneumonia

In recent years several careful studies of the sputum from cases of pneumonia have shown that a change has probably occurred in the aetiology of the disease. Studies in London (Crofton *et al.*, 1951), Glasgow (Grist *et al.*, 1952), and Sheffield (Stuart-Harris, 1953) showed that some 20 to 50% of patients with clinical and radiological evidence of pneumonia failed to yield pathogenic bacteria in the sputum (Table I). Yet the response to treatment in these patients was not obviously different from that in patients whose sputum contained an organism such as the pneumococcus. The decline in the bacteriologist's ability to identify the cause of presumed bacterial pneumonia is perhaps a cause of the clinician's discontent at being told to "take a specimen and wait for the sensitivity test." It is certainly unjustifiable to delay therapy in patients with signs of consolidation and one must judge the question much more from the standpoint of the degree of general illness than by whether or not bacteria have been identified.

However, the bacteriological results already quoted are the best guide that we have for the selection of appropriate chemotherapy. Compared with the importance of the pneumococcus and the staphylococcus other bacteria are relatively infrequent causes of pulmonary consolidation though they cannot be wholly ignored. Apart from influenza epidemics, it is clear that the pneumococcus still predominates over all other identifiable bacteria, and even during influenza it causes the majority of the pneumonic complications.

The antibiotic sensitivity of the pneumococcus is a broad one, and the various clinical trials which have been carried out both in this country (Antibiotics Clinical Trials Committee, 1951) and the U.S.A. (Dowling and Lepper, 1951) have failed to show much difference between the efficacy of penicillin and the tetracycline group of antibiotics or of chloramphenicol in pneumococcal pneumonia. Although many clinicians who work in hospital still prefer penicillin there is no doubt that the tetracyclines are often prescribed in domiciliary practice because of their convenience in administration. Nevertheless they are more toxic than penicillin, and pride of place should still go to the latter, particularly for those who are gravely ill.

Why do not all cases of pneumococcal pneumonia recover? The mortality of 5% or more which is still recorded is unquestionably due to host factors which are of such importance in pneumonia. Long before the sulphonamide era the significance of age, of previous chronic disease of the lung or coexisting disease of the heart, and of the duration of disease before treatment was realized during attempts to evaluate serum therapy for pneumonia. Such factors are still of importance to-day (Van Metre, 1954), and must not be forgotten whenever it seems that antibiotic therapy is failing in spite of an apparent sensitivity of the bacteria in the sputum to the drug. Fortunately antibiotic resistance has not yet become evident in the case of the pneumococcus.

Staphylococcal Pneumonia

The bacteriological results obtained in cases of pneumonia during the influenza epidemics of 1949 and 1951 (Stuart-Harris, 1953), which were abundantly confirmed during the Asian influenza epidemic, stressed the importance of the *Staphylococcus aureus*. Although staphylococcal pneumonia can occur apart from influenza virus infection, it is the combined infection of the two organisms which presents such a formidable therapeutic problem. This is well shown by analysis of the findings in fatal cases of Asian influenza (Table II). A majority of the cases submitted to post-mortem examination showed a pneumonia often haemorrhagic in type or else a tracheobronchitis. The staphylococcus alone or combined with other organisms was found in 62% of the British cases and in 67% of the Dutch patients. It is clear that influenzal-staphylococcal pneumonia is a formidable problem from the

TABLE I.—*Aetiology of Pneumonia*

Author	No. of Cases	Pathogenic Organisms Identified in the Sputum					No Aetiology Determined
		Pneumococcus	Staphylococcus	H. Streptococcus	Friedländer's Bacillus	Other*	
Crofton *et al.* (1951)	110	29 (26·3%)	10 (9·1%)	—	—	19 (17·2%)	52 (47·2%)
Grist *et al.* (1952)	129	84 (65·1%)	—	—	—	10 (7·7%)	35 (27·1%)
Stuart-Harris (1953) Non-influenzal period	130	104 (80%)	7 (5·3%)	2	0	—	25 (19·2%)
Stuart-Harris (1953) Influenzal period	166	114 (68·6%)	33 (29%)	3	3	—	20 (17·5%)

* The basis for classification of this group differed in the two series quoted.

TABLE II.—*Bacteriology in Fatal Cases of Asian Influenza*

Country	Author	No. of Cases	Pneumococcus		Staphylococcus		H. Streptococcus		*H. influenzae*		Non-pathogenic Organisms Only	Sterile
			Alone	Combined	Alone	Combined	Alone	Combined	Alone	Combined		
Britain	P.H.L.S. (1958)	447	16	12	217	71	3	20	7	23	101 (21·6%)	41 (8·8%)
					61·8%							
Holland	Hers *et al.* (1957)	103	3		69		1		1		*E. coli* 7	22

therapeutic point of view and at least four reasons can be discerned for this.

1. The staphylococcus may be resistant to penicillin initially or may become resistant after treatment has begun. 35% of the staphylococci isolated from patients dying before or within 48 hours of admission to hospital were resistant to penicillin in the recent British series (Public Health Laboratory Service, 1958). Treatment of such penicillin-resistant staphylococci can of course be attempted with either a tetracycline or an erythromycin antibiotic. But the results are much poorer than with penicillin in appropriately sensitive infections.

2. The actual mass of invading cocci, which is considerable, is largely located on the surface of the bronchi and bronchioles in a web of necrotic mucosa, though it later spreads to the alveoli. There is no evidence of bacteriaemia, and metastatic abscesses are not found at necropsy. It seems probable that, at least in the early stages, the infection is relatively inaccessible to antibiotics.

3. Often death appears to be due to the toxic effects of the infection. It is not possible to separate the effects of staphylococci from those of virus, but the considerable number of fatal cases either with sterile lungs or with non-pathogenic bacteria during the recent epidemic is an eloquent testimony of the virulence of the virus alone. Antibiotics are of course useless for bacterial toxaemia, and the effect of the latter on the circulatory system is thus unchecked by treatment. There is no antibiotic yet available against influenza virus.

4. The speed of advance of the infection is often totally unexpected to the clinician, who finds purple lips and panting dyspnoea in a patient who, a few hours before, may not have felt ill enough to go to bed. Absence of pleural pain is another reason for the failure to understand the gravity of the attack in the early stages of staphylococcal pneumonia when treatment ought to begin.

These four reasons fully exemplify the principles which govern success or failure of antibiotic treatment. Moreover, the dangers of indiscriminate antibiotic treatment, at least in cases of influenza, have been stressed by Walker *et al.* (1958) in their analysis of staphylococcal pneumonia. They point out that too broad a spectrum of antibiotic cover may so sterilize the upper respiratory tract that resistant organisms may fill the vacuum created. Cases of influenza may thus become secondarily infected by hospital staphylococci after admission, and these are usually resistant to penicillin and perhaps to other antibiotics as well. In regard to the treatment of patients already infected with staphylococci on admission, it is of the utmost importance to recognize the infection as soon as possible. For this purpose the Gram-stained film of sputum has been useful in my own hands, though it is not infallible and must be followed by cultivation of the sputum and tests of sensitivity to penicillin and the other antibiotics. A combination of penicillin and streptomycin during the first two days after admission can be modified, if necessary, when the results of sensitivity tests are available. If the illness is of a fulminant character erythromycin should be combined with these antibiotics in case the infection is caused by a penicillin-resistant staphylococcus. The question of ancillary treatment by steroids or by staphylococcus antitoxin appears almost irrelevant by the side of the vitally necessary antibiotics. Neither method has really justified its claim for inclusion in the therapeutic regime, and steroids may be positively harmful.

Other Forms of Bacterial or Fungal Pneumonia

Space forbids a detailed discussion of such pneumonias as those due to Friedländer's bacillus, *E. coli*, and fungi of the *Aspergillus* or *Candida* species. Their existence is a justification for continued careful examination of the sputum in cases of pneumonia, and particularly if no immediate response is occurring to treatment with penicillin or the sulphonamides. Streptomycin is a useful antibiotic for pneumonias due to Gram-negative bacteria of the coliform group, and antifungal antibiotics such as nystatin or amphotericin B may be useful in fungal cases, which sometimes develop in the wake of bacterial infections treated by the broad-spectrum antibiotics.

Virus Pneumonias

A great deal has been written and talked about the subject of virus pneumonias in the past few years. Apart from fulminant influenza, psittacosis, and Q fever, the other forms of virus pneumonia are benign, almost trivial, self-limiting conditions which usually require no specific treatment at all. These benign pneumonias are usually diagnosed only when the radiologist reports an unsuspected opacity of the lung fields of a hazy or mottled character in a case previously diagnosed as P.U.O. or acute bronchitis. It seems likely that this is a relatively uncommon disease in civilian practice apart from occasional outbreaks in schools, though it is not rare in Service communities. The diagnosis is often made on grounds of probability and without radiological confirmation in patients with an acute lower respiratory infection which is not responding rapidly to antibiotics. It is a diagnosis which should be resisted lest a more serious condition such as bronchial carcinoma may be ignored. It is also important to avoid the concept of virus infection simply because pathogenic bacteria have not been found in the sputum.

If, however, the radiological picture is suggestive, if general signs of bronchitis are present, or serum agglutinins against group O red cells are found in tests carried out at 4° C., then the diagnosis of atypical or virus pneumonia can be upheld. Even the absence of cold agglutinins is not an absolute bar to the diagnosis, for occasional cases without such agglutinins and due to the adenoviruses have now been described. But the published evidence on the treatment of these infections by the tetracyclines, chloramphenicol, or even by erythromycin (Wolf and Brown, 1956) is on the whole in favour of withholding antibiotics. Control series of patients untreated by antibiotics do just as well as those receiving the latter.

The same cannot be said for psittacosis, of which the variety contracted from parrots is a serious condition. Penicillin and the tetracyclines are both active against psittacosis virus in the laboratory. Q fever due to *Rickettsia burneti* is also said to respond to the tetracyclines, but the organism is less sensitive than the rickettsiae of the typhus fevers. Both psittacosis and Q fever are relatively rare conditions in civilian practice in Great Britain.

Treatment of Acute Bronchitis and Bronchiolitis

The fact that the number of patients with consolidation of the lungs met with in practice or in hospital is only a fraction of the total number ill with acute chest disease has already been stressed. The other infections of the lower respiratory tract consist chiefly of cases of acute tracheobronchitis and of bronchiolitis. The causes of these infections are largely unknown and their response to treatment is equally uncertain.

The problem is greatest in infants and young children in whom the prevalence of bronchitis or bronchiolitis rises during winter epidemics of acute respiratory infection. Such epidemics as are associated with the influenza viruses form only a portion of the total, and there have been several accounts of outbreaks in children unconnected with adult epidemics (Garrow and Fawcett, 1953). There is little doubt that these outbreaks are due to viruses, but there is no certain knowledge of the nature of the latter. Since the discovery of the adenoviruses in 1953, an association has been found between certain of the serological types of adenoviruses and epidemics of pharyngitis with lower respiratory disease as well in children and adults. But such infections do not account for much of the toll from bronchitis.

The next discovery was of the croup or laryngo-tracheo-bronchitis virus recovered by Chanock (1956) in the U.S.A., and by Beale *et al.* (1958) in Toronto. This virus accounts for some cases of obstructive laryngo-tracheo-bronchitis in infants, but it seems unlikely to be a cause of much disease in adults. The J.H. virus of Price (1956), the " U " virus from Uppsala (Philipson, 1958), and the haemagglutinating viruses recovered by Chanock *et al.* (1958) were discovered far too recently for an opinion to have been formed of their relation either to the common cold or to minor respiratory infections. It seems likely that any or all of these viruses may at times be associated with cases of bronchitis or of bronchiolitis. None are known to be sensitive to antibiotics, and it is small wonder that the latter are ineffective against human acute respiratory disease uncomplicated by bacterial infection.

In practice the investigation of acute bronchitis and bronchiolitis in tiny babies and young children is hampered by the difficulty in obtaining a specimen of sputum. Morrison *et al.* (1957) used cough swabs as well as pernasal and throat swabs. A range of organisms similar to that found in pneumonia was recovered from cases of bronchitis, but no pathogenic bacteria were recovered from 23 of 62 cases (37%) of bronchitis or from 27 of 78 cases (34%) of segmental pneumonia and bronchopneumonia. Even when pneumococci, staphylococci, haemolytic streptococci, or *Haemophilus influenzae* are obtained from swabs there is no assurance that they are concerned in the chest disease such as would have been likely if they had been demonstrated in sputum. Nevertheless, it is probable that few clinicians are prepared to withhold antibiotics in the treatment of an acute chest infection in children unless the degree of illness is trifling. The threat of pneumonia and of possible damage to bronchi at a tender age is a justification for therapy even though the latter can only affect a secondary infection. But it is certainly unjustifiable to expose the child to any risk of upset by such therapy, and penicillin or a drug of the tetracycline group is all that should be used.

In adults the problem of chronic chest disease, of chronic bronchitis and emphysema, and of bronchiectasis is intermingled with that of acute bronchitis. For, in addition to cases of acute bronchitis in previously healthy persons, the exacerbations of illness in cases of chronic bronchitis are distressingly common and a serious cause of economic disturbance, particularly in industrial areas.

There is some variation in the findings of different workers in this country concerning the relative frequency of the different nasopharyngeal bacteria found in the sputum of patients with chronic bronchitis (Table III). All are agreed that the pneumococcus, *H. influenzae*, and *Staphylococcus aureus* lead all others in frequency and also that the greater the degree of purulence of the sputum the greater the number of bacteria likely to be present. But it is impossible to believe that bacteria are the primary cause of chronic bronchitis, and even acute exacerbations are often initiated by acute upper respiratory infections presumably caused by viruses.

It is reasonable to ask for a precise statement concerning the role of chemotherapy in chronic bronchitis and bronchiectasis. Antibiotics are widely used to treat acute exacerbations of illness; they diminish the amount of sputum and the frequency of coughing. Penicillin either alone or combined with an antibiotic which is more effective than penicillin against *H. influenzae* is the treatment of choice. Oxytetracycline, erythromycin, and chloramphenicol are all active against *H. influenzae* and have all been used in hospital practice. Chloramphenicol probably reduces the amount of sputum most effectively and is preferred to tetracycline drugs for the treatment of acute exacerbations by some (Douglas *et al.*, 1957; Ioannidis and Murdoch, 1957). But the tetracyclines are less hazardous even for short periods of treatment and are also less likely than chloramphenicol to cause an increase in dyspnoea due to excessive viscidity of the sputum in cases of emphysema. Because the exact species of organism associated with bronchitis exacerbations varies from place to place and from time to time, a watch on the sputum is essential. Simpson (1958), for instance, remarked on the recent rise in importance of the staphylococcus in bronchitis following the epidemic in Asian influenza.

An entirely different way of using chemotherapy in patients with chronic chest disease is by long-term administration to prevent relapses—that is, prophylactic administration of the drugs as soon as an upper respiratory infection begins. The evidence from the Brompton Hospital workers (Helm *et al.*, 1954, 1956; May and Oswald, 1956) suggests that oxytetracycline is a useful drug for prolonged therapy in chronic bronchitis. Other workers in London (Elmes *et al.*, 1957) and in Leeds (Edwards *et al.*, 1957) are more doubtful. The case for prophylaxis with antibiotics is not proved. Such therapy is expensive, and in my view hazardous because it encourages the colonization of the respiratory tract with antibiotic-resistant organisms. We should certainly do nothing to impair the value of treatment for acute relapses of infection which may precipitate heart failure or may lead to death from respiratory insufficiency. The best way to use chemotherapy in patients with chronic

TABLE III.—*Cultivation of the Sputum in Cases of Chronic Bronchitis**

Place	No. of Patients	No. of Specimens	Pneumococci	*H. influenzae*	*Str. haemolyticus*	*Staph. pyogenes*	Friedländer's Bacillus	Coliform
Sheffield (Stuart-Harris, 1953) ..	113	172	87 (50·5%)	26 (15%)	8	20 (11·6%)	2	5
Albany, N.Y. (Brown *et al.*, 1954)	20	83	61 (73·5%)	42 (50·6%)	5	2	—	12 (14·4%)
Brompton Hospital { May (1953) ..	54	54	31 (57·4%)	14 (25·9%)	—	7	3	4
Brompton Hospital { .. (1954) ..	30	—	6 (20%)	27 (90%)	—	—	—	—

* After Stuart-Harris and Hanley (1957).

chest disease, therefore, is to limit antibiotics to acute phases of illness or to short periods of treatment in those who have undergone slow deterioration as a result of insidious exacerbation of symptoms. In both instances, antibiotics form only a part of the therapeutic armamentarium—a very different statement from the role of antibiotics in pneumonia.

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"United Kingdom exports of drugs and medicines in 1958 did not quite reach their record figure of £39.6m. in 1957, but they were the second highest ever at £37.8m. Antibiotics accounted for £8.3m., miscellaneous proprietary medicines (including those for supply on prescription) £10.6m., and vitamins £2.5m. Exports of alkaloids, aspirin, synthetic antimalarial drugs, ointments and liniments, and sulphonamide preparations all exceeded £1m. Australia was once more the chief overseas market (£3.3m.), followed by Nigeria (£2.1m.). Next came New Zealand (£1.9m.), the Union of South Africa (£1.8m.), India (£1.7m.), the Irish Republic (£1.6m.), and Pakistan (£1.5m.). For the first time exports to the United States of America exceeded £1m., and those to Canada were only just under this figure. In each case the increase over the previous year was in the region of £250,000. Exports to Egypt rose from £84,000 in 1957 to £494,000, and it is hoped that more of this important market will be regained.

"The effect of the financial crisis and increasingly stringent import policy in India was shown by a decrease of exports from £2.9m. to £1.7m."—*The Association of British Pharmaceutical Industry: Annual Report, 1958-9.*

CHEMOTHERAPY OF PULMONARY TUBERCULOSIS*

BY

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The right use of modern methods of chemotherapy now makes it possible to aim at 100% success in the treatment of pulmonary tuberculosis. In all countries from which figures are available there has been a dramatic fall in deaths from tuberculosis since the introduction of chemotherapy in 1947–8. The fall has been well marked in England and Wales but even more impressive in Scotland, where the mortality was previously rising (Fig. 1). That the widespread use of proper methods of chemotherapy can have an effect also on the number of fresh cases of tuberculosis is well shown from the Edinburgh figures (Fig. 2). At the beginning of 1954 an integrated service for tuberculosis was introduced in Edinburgh, with the result that proper methods of chemotherapy were used for all patients requiring treatment. The waiting-list for admission to hospital, which reached a peak of 375 in March, 1954, was virtually abolished during the succeeding year. Nearly all sputum-positive patients were admitted to hospital, and scarcely any were discharged with a positive sputum. Fig. 2 shows how, as a result, a steadily rising incidence of new cases was converted to a dramatic fall. Since March, 1955, there has never been more than 1% of the patients on the Edinburgh Tuberculosis Register out of hospital with a positive sputum.

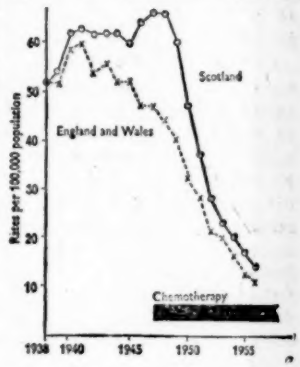

FIG. 1.—Mortality from respiratory tuberculosis, 1938–56.

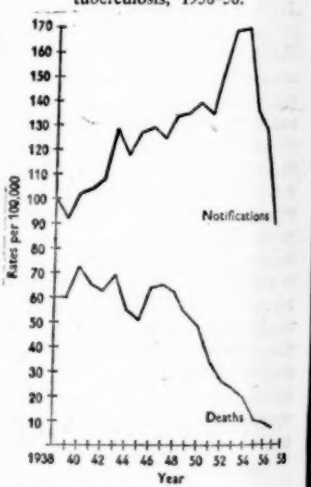

FIG. 2.—Edinburgh: death and notification rates for pulmonary tuberculosis since 1938.

Prophylactic Chemotherapy

There are three groups in which the question of prophylactic chemotherapy might be considered.

1. *Children with a positive tuberculin reaction as the only evidence of infection.*—A controlled trial of

*Read to a Plenary Session at the Annual Meeting of the British Medical Association, Birmingham, 1958.

prophylactic isoniazid therapy was recently carried out in the United States (U.S. Public Health Service, 1957). In children with a positive tuberculin reaction, but no overt disease, aged under 1 year, later clinical tuberculosis developed in 3.3% of those treated with dummy tablets compared with 0.7% in those treated with isoniazid. This is a big difference but a low complication rate. It probably just justified chemotherapy. Over the age of 1 year the complication rate was so low that it is probably best to watch the child carefully and treat as soon as there is any clinical or radiological manifestation of disease. The complication rate is much higher if there is any abnormality in the chest *x*-ray picture, and we think all such patients should be treated. We would use isoniazid and P.A.S. (*para*-aminosalicylic acid) and not isoniazid alone, in order to avoid drug resistance.

2. *Adolescents with strongly positive tuberculin reactions but no detectable disease.*—Studies by the Medical Research Council (1956) in connexion with the use of B.C.G. in school-leavers suggested that children aged 13 to 14 with strongly positive tuberculin reactions, but with a normal chest *x*-ray picture, were at a higher risk of developing pulmonary tuberculosis than were children with weaker positive reactions. The annual incidence was 1.75 per 1,000 children in the Medical Research Council trials. This risk is so relatively small that it is probably better to keep all such children under observation and to treat them only if some clinical manifestation of tuberculosis is found.

3. *Lung lesions of doubtful activity.*—Another group of cases in which treatment may be controversial comprises those with lesions of doubtful activity picked up on mass radiography. In the last three years the Tuberculosis Society of Scotland (1958) has been carrying out a controlled trial on such patients, one group being kept under observation in the ordinary way and the other being given, so to speak, "prophylactic" chemotherapy with P.A.S. and isoniazid for a minimum of six months. Over a two-year follow-up period there was a breakdown rate of approximately 17% in those undergoing observation only, compared with 8% in the group that was supposed to be treated. But all the definite breakdowns in the so-called treated group were in patients who had failed to take their chemotherapy as advised. This finding emphasizes the great difficulty in ensuring that all patients on out-patient treatment take their chemotherapy as directed. The conclusion is that doubtful lesions need not be treated as a routine, though certain cases at particular risk deserve treatment. The remainder should be kept under careful observation and treated only if there is deterioration.

Where Chemotherapy Should be Given

Active Tuberculosis.—So far we have been discussing circumstances in which there might be some doubt about the necessity for chemotherapy. This arises only when it is uncertain whether the disease is active or not. In the presence of active tuberculous disease anywhere in the body there is not the slightest doubt that chemotherapy is indicated in all cases.

Mild Cases.—A few years ago there was no doubt that a case of tuberculosis was best treated in hospital or sanatorium, at least in the first place. When there was a shortage of beds many patients had to be treated at home, but it was usually admitted that this was second best. The main reason for hospital or sanatorium treatment was the necessity for strict bed rest. After seeing the remarkable effect of chemotherapy a number of physicians came to question the necessity of bed rest, at least in mild cases. In order to answer this question the Tuberculosis Society of Scotland has carried out a carefully controlled trial from 1954 (Kay, 1957). The trial concerned patients whose main abnormality was a radiological change, who had no important symptoms, and whose sputum was negative on direct smear or concentration. Patients whose sputum, laryngeal swabs, or gastric lavages later turned out to be positive on culture were not thought to constitute a significant danger to their fellows (Shaw and Wynn-Williams 1954; Van Zwanenberg, 1955; Hertzberg, 1957).

The cases in the trial were divided at random into two groups, one of which was treated by classical means with bed rest and chemotherapy, and the other with the same chemotherapy but continuing at their normal work. It was found that the frequency of radiological improvement, and its degree, were just as high in those treated at work as in those treated on bed rest. It therefore seems that the co-operative patient who is likely to take his chemotherapy conscientiously, whose sputum is negative, and who has no significant cavitation can be treated at work. The economic and social gain both to the patient and to the community is obviously enormous. However, such a method of treatment is to be undertaken only when it is certain that the patient will prove entirely reliable and when the physician in charge is prepared to take immense trouble to ensure that he does exactly what he is told and is kept under the closest supervision. In Edinburgh 40–50% of newly diagnosed patients are now treated at work.

Infectious Cases.—We now think all patients with positive sputum should be treated in hospital until their sputum has converted to negative. Many will only have to stay in hospital for three to four months.

Methods of Chemotherapy

Drug Resistance

The greatest disaster that can happen to a patient with tuberculosis is that his organisms become resistant to two or more of the standard drugs. Fortunately we can prevent the emergence of drug resistance in virtually all cases if we take enough trouble to ensure that the best drug combinations are prescribed and that the patient takes them as directed. It is often not realized how venial a sin can result in ultimate disaster. It might be suggested that giving a risky combination of drugs, or even giving a drug alone, will not matter if it is only for a short time. It is true that it may not matter in a number of patients, but in some it can matter very much and may make all the difference between survival and death.

The development of drug resistance may be a tragedy not only for the patient himself but for others. For he can infect other people with his drug-resistant organisms. In such patients the disease would not be sensitive to the drug in question. A recent survey by the Medical Research Council (Fox *et al.*, 1957) in various clinics all over the country has shown that no less than 5% of newly diagnosed patients were infected with organisms resistant to at least one of the three main drugs. If physicians come to apply thoroughly the present knowledge about preventing drug resistance, this percentage should steadily diminish.

Good Chemotherapy

If proper chemotherapeutic combinations are used for an adequate time it should be possible to convert the sputum to negative in all patients infected with bacilli sensitive to the standard drugs. In Edinburgh a patient with disease severe enough to require admission to hospital initially receives all three standard drugs. All three drugs are given in case he has been infected with tubercle bacilli resistant to one of them. The other two will then not only be active against the disease but will prevent further resistance developing. Infection with bacilli resistant to two of the main drugs is fortunately rare.

In patients under the age of 40 we give streptomycin, 1 g. daily, together with sodium P.A.S., 5 g. three or four times a day, and isoniazid, 100 mg. twice daily. Over the age of 40, as daily streptomycin may give rise to vestibular disturbances, we give streptomycin, 1 g. three times a week, with P.A.S. and isoniazid as before. This does carry a theoretical risk. A patient infected with P.A.S.-resistant bacilli would virtually be receiving intermittent streptomycin with daily isoniazid. It might be more rational to give 0.5 g. of streptomycin daily. But so far we have had no reason to regret our present practice.

Resistance tests on cultures taken before the start of treatment become available in two or three months. In younger patients, if the bacilli prove to have been sensitive to all three drugs, we omit the P.A.S. and give daily streptomycin and isoniazid so long as the patients are in hospital. Intermittent streptomycin with daily isoniazid is a risky combination, so in older patients we continue streptomycin three times weekly, with daily P.A.S. and isoniazid as before.

When the patient is discharged from hospital, or in mild cases which do not require admission, it is most convenient to use an oral combination of drugs. The standard combination is 5 g. of sodium P.A.S. and 100 mg. of isoniazid, both given twice daily. For out-patients both drugs are given in the same cachet so as to ensure that they do not take one drug without the other. Unfortunately, we have found that if patients fail to take the full number of cachets isoniazid-resistant organisms may emerge in some cases (J. McD. Simpson, to be published). In such cases the lower dose of P.A.S. is apparently insufficient to prevent isoniazid resistance even when the isoniazid is reduced *pari passu*. It should be added that we do not use the combination of P.A.S. and isoniazid as initial treatment in patients with severe disease and large bacillary populations. Unpublished information from elsewhere suggests that drug resistance and treatment failure may result in a few such patients.

Sputum Conversion

Fig. 3 (Crofton, 1958) represents an analysis of sputum conversion in all my personal patients with pulmonary tuberculosis admitted to hospital in the five years 1952–6. The graph includes only patients whose sputum was positive and whose organisms were sensitive to at least two of the three main drugs. Four patients are omitted from the graph. Three died from other diseases before the sputum had converted to negative but while still excreting drug-sensitive organisms. The fourth was infected with P.A.S.-resistant bacilli, and was treated (in a Medical Research Council trial), before the resistance was known, with P.A.S. and isoniazid. His bacilli also became isoniazid-resistant, and his sputum was made negative by surgery under cover of streptomycin *plus* oxytetracycline.

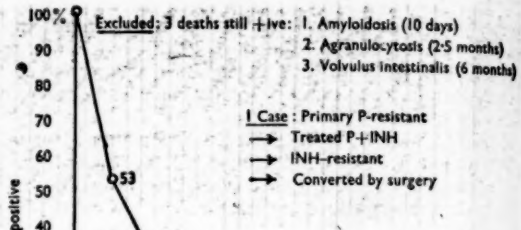

FIG. 3.—Sputum conversion with chemotherapy, 1952-6. 240 cases with bacilli sensitive to at least two drugs. P=P.A.S. INH=Isoniazid. Periods given in parentheses indicate the time after beginning of treatment at which death occurred. Reproduced from Crofton (1958) by permission of the editor of the *American Review of Tuberculosis*

More than 40% of these cases were classified as "far advanced." It will be seen that sputum conversion occurred in all patients, about 80% having converted by the third month of treatment, 96.5% by the sixth, and all by the tenth month.

Duration of Chemotherapy

It is our view that all patients with tuberculosis require to continue chemotherapy for at least one year, those with severe disease up to two years—occasionally longer. If we accept that we should convert the sputum in all cases of tuberculosis with initially sensitive organisms, it is clear that our aim must be to continue chemotherapy for long enough to prevent relapse. We have determined the optimal duration of chemotherapy by studying the relapse rate after different periods of chemotherapy (Ross *et al.*, 1958). In Fig. 4 are given the relapse rates for all 259 patients with pulmonary tuberculosis admitted to Edinburgh hospitals in 1953 who were discharged with a negative sputum. Of these, 241 had not been shown to harbour tubercle bacilli resistant to more than one of the three main drugs. It will be seen that among the few and who received less than three months' chemotherapy the relapse rate was no less than 36%. In those patients who were thought to have inactive disease

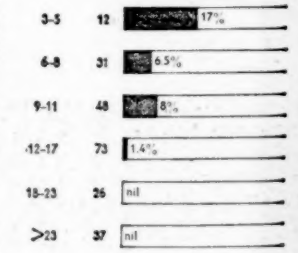

FIG. 4.—Length of chemotherapy and release in 259 cases of pulmonary tuberculosis admitted in 1953. Follow-up, December, 1956. The figures are derived from Ross *et al.* (1958). They comprise all patients admitted to Edinburgh hospitals with pulmonary tuberculosis in the year 1953.

who received three to five months' chemotherapy the rate was 17%. After this the rate dropped briskly, but there was an appreciable relapse rate up to one year. However, among the 136 patients, mainly with more severe disease, who received more than one year's chemotherapy there has so far been only one relapse, and among those who received more than 15 months' no relapse at all. The few patients with resistant organisms whose sputum had been converted by various measures suffered a relapse rate of 22%.

The investigation carried out by some of my colleagues on the isolation of tubercle bacilli from resected lungs yielded results remarkably consistent with our figures for relapse Although among those with resistant organisms bacilli could be isolated from the lungs even with chemotherapy continued up to two years, among those with sensitive organisms the isolation rate fell steadily with the duration of chemotherapy. Among patients who had received more than one year of chemotherapy there were only two positive isolations from 101 lung lesions. No tubercle bacilli were isolated from any of the 22 lesions from patients who had received more than 18 months' treatment (Stewart *et al.*, 1956, with later additions).

At present our follow-up studies of patients treated with prolonged chemotherapy extend only for five to six years. It may be that the relapse rate will increase with the course of time, but so far there is no tendency for it to do so.

Relation to Other Treatment

Long-term chemotherapy has been so successful that it has largely ousted other methods of treatment. As already mentioned, bed rest has greatly diminished in importance, while collapse therapy has been largely abandoned and the necessity for surgery very greatly reduced. It may still be reasonable to resect large residual cavities which are liable to secondary infection, provided there is no major operative risk; but the two main residual indications for surgery are the uncooperative patient, who possibly cannot be relied on to continue taking his chemotherapy over long periods, and the patient whose organisms have been made drug-resistant by the use of unsatisfactory combinations of chemotherapy or by failure to carry out instructions

Unreliable Methods of Chemotherapy

In the past the most frequent cause of drug resistance was the administration of one of the three main drugs alone. In this country at least this is now seldom done. The most common error is to give intermittent streptomycin, two or three times a week, together with *either* daily P.A.S. *or* daily isoniazid. Both of these combinations will be successful enough in the majority of cases, but in an important minority they result in drug resistance. A less frequent error is to combine daily streptomycin with an inadequate dose of P.A.S. Studies by the Medical Research Council (1952) showed that the dose of sodium P.A.S. must be 20 g daily if drug resistance is to be prevented in a high proportion of cases. Such a high dose is not easy to tolerate, and streptomycin and P.A.S. are now seldom used except in patients whose organisms are already isoniazid-resistant.

One should beware of using substitutes for P.A.S. or isoniazid which are alleged to be better tolerated. Some have very little action or are poorly absorbed. Some marketed combinations or mixtures of drugs provide inadequate defence against drug resistance.

Treatment of Patients with Drug-resistant Bacilli

The treatment of patients who, either because of poor combinations of drugs or because they have failed to take the drugs as directed, harbour drug-resistant tubercle bacilli is a matter of considerable skill, requiring the closest co-operation between physician, specialist, bacteriologist, and surgeon. For these patients various forms of "salvage" chemotherapy have to be employed. Such drugs are in general much less effective than the standard ones and also more toxic and more expensive. Chemotherapy alone can seldom be expected to achieve long-term results. If possible the major lesion or lesions should be extirpated with surgery The optimum combinations to use in a particular case require careful study. The drugs at present used for "salvage" chemotherapy are various combinations of the following: pyrazinamide, cycloserine, viomycin, tetracycline, and perhaps "1314." In far-advanced cases the results are greatly inferior to those achieved by standard chemotherapy in patients with sensitive organisms

Corticosteroids

Controlled studies by the Tuberculosis Society of Scotland (1957) have shown that corticosteroids in the form of prednisolone have a definite effect in hastening improvement when given with satisfactory combinations of drugs. Although initial progress is more rapid, so far there is no evidence that the ultimate result is any better. At present we feel that the corticosteroid drugs are indicated only in patients who are very ill when admitted to hospital. In such patients prednisolone certainly rapidly increases the sense of well-being and improves the toxic state. It may keep some otherwise hopeless cases alive until chemotherapy takes effect.

Conclusions

In conclusion, it is proper to emphasize that it is now possible to aim at 100% success in the treatment of pulmonary tuberculosis caused by organisms sensitive to the standard drugs It is true that there may still be an occasional death from cor pulmonale in patients with badly damaged lungs, from post-operative complications, or in patients moribund on admission. But these should be very rare Some patients with advanced and chronic disease, even though the tuberculosis is arrested, will be left with permanent impairment of respiratory function. Nevertheless the vast majority make a good recovery and should have no relapses. Unfortunately, such results are attainable only by exercising the greatest care in prescribing the right combination of drugs, by handling the patient so that he continues to take his chemotherapy conscientiously over long periods of time, during much of which he is feeling perfectly well, and by carrying out the most careful drug-resistance tests in those in whom there is any reason to suspect that resistance may have occurred. The slightest error on the part of either doctor or patient may result in disaster. In no disease is the result of conscientious doctoring more rewarding. In none is the result of carelessness or ignorance more tragic for the patient.

Summary

Since the introduction of chemotherapy for the treatment of pulmonary tuberculosis in 1947–8 there has been a dramatic fall in mortality in all countries from which figures are available. This has been particularly impressive in Scotland, because there the rate was previously rising.

The use of chemotherapy is now beginning to reduce the morbidity of the disease. In Edinburgh since 1954, when a reorganization of the services ensured that all patients received effective chemotherapy, there has been a dramatic fall in new notifications: the figures for 1957 were only 54% of those for 1954.

"Prophylactic" chemotherapy, given to individuals in whom a positive tuberculin reaction is the sole evidence of disease, is probably justifiable only in the case of very young children.

It has been shown in a carefully controlled trial that patients with mild and relatively uninfectious pulmonary tuberculosis can be as effectively treated with chemotherapy while working as with chemotherapy while resting in bed. Nevertheless this should be done only if the patient can be relied on to take his chemotherapy as directed, and if he is kept under very close supervision.

The greatest tragedy that can happen to a tuberculous patient is that his tubercle bacilli become resistant to the standard drugs. This can virtually always be avoided by proper methods of chemotherapy, but minor errors of commission or omission may be disastrous.

With proper methods of chemotherapy the sputum should always be converted to negative provided the patient's bacilli are initially sensitive to the standard drugs. This was achieved in all of 240 personal cases treated in the five years 1952–6.

To avoid relapse chemotherapy should be continued for a minimum of one year and in most patients for 18 months to two years, occasionally longer.

At present corticosteroids are indicated only for very ill patients.

The conclusions in this article are based largely on the work of my colleagues in Edinburgh, Drs. I. W. B. Grant, N. W. Horne, J. D. Ross, Sheila Stewart, A. T. Wallace, and J. Williamson, and also on that of many past and present assistants, of the members of the Research Committee of the Tuberculosis Society of Scotland, and of the Medical Research Council. Much of the research work in Edinburgh was supported by generous grants from the Royal Victoria Hospital Tuberculosis Trust.

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The International Atomic Energy Agency, on which Great Britain is represented, has issued a booklet entitled *Safe Handling of Radioisotopes* (pp. 99). It gives detailed instructions on the safe storage, use, and disposal of radioactive substances, and has been prepared "after careful consideration of existing national and international codes of radiation safety." The authors hope that it will be helpful "particularly to small-scale users who may not have direct access to other sources of information." Price 6s. net from the Agency at Kärntner Ring 11, Wien I, Austria.

THE NATURAL HISTORY OF CEREBROVASCULAR DISEASE

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Cerebrovascular disease is one of the commonest causes of death in the older age groups of the population, and greatly exceeds other causes such as cardiovascular disease and bronchial carcinoma, which of late have attracted more attention than the somewhat pedestrian "stroke" (Elkington, 1958). Despite the frequent occurrence of the disease, knowledge of its natural history is surprisingly scanty. In the textbooks attention is largely confined to the immediate prognosis of the acute cerebrovascular accident, and little account is given of the long-term future of the patient with cerebrovascular disease. One of the reasons for this lack of knowledge is that there is little agreement on the exact pathological processes which afflict the cerebral vessels, and the relationship of these processes to the protean clinical manifestations. Recently, attempts have been made to treat cerebrovascular disease by various methods, including anticoagulant and hypotensive drugs. One of the consequences has been to emphasize our lack of accurate knowledge of the natural history of the disease with which to compare the results in treated groups of patients. There are, however, some studies which help to fill this gap in our knowledge.

Rosling (1934) observed that of 69 patients with hypertension who had experienced a stroke more than eight years previous to his study, 26 had died of cerebrovascular disease and four of heart disease. Pincock (1957) followed 117 male patients in whom a clinical diagnosis of cerebral thrombosis had been made, and found that of the 101 who survived the acute attack 55 died within the next seven years, but in his series more commonly from cardiac causes. He also noticed that those who died had experienced multiple accidents, in contrast to the infrequency of further accidents in the survivors. Pierson and Hoobler (1957) observed among 71 patients with hypertension below the age of 50 years that 50% died within five years of having had what they called an attack of "transient encephalopathy," and that two-thirds of the deaths were due to cerebrovascular accidents. Currier, Giles, and Westerberg (1958) followed 62 patients with a clinical diagnosis of thrombosis of the posterior inferior cerebellar artery and found that 46% of the patients had died within five years. Lindgren (1958) followed 65 cases of occlusion of the internal carotid or middle cerebral artery or its branches and found that 22 of the patients had died within two years. Kincaid-Smith, McMichael, and Murphy (1958) observed 79 patients with malignant hypertension in whom there was evidence of neurological involvement. There were 65 patients in whom the cause of death was ascertained, and in 33 of these it was due to a neurological cause. However, patients who survived a neurological incident were no more liable to die of a further incident than

were those patients who had not experienced such an episode.

The most important recent attempts to arrest the progress of cerebrovascular disease have been by anticoagulant therapy. Thus in 1955 Millikan, Siekert, and Shick reported the results of treating 26 patients with insufficiency or thrombosis of the basilar arterial system by means of anticoagulants. They assessed the results by comparing them with a group of control patients. Similarly, Fisher (1958) treated 58 patients with thrombosis of various cerebral arteries by means of anticoagulants, and compared their progress before and after the start of treatment. This latter method of assessment is based upon the assumption that in the natural course of the disease those who survive early incidents are likely to continue having further incidents, but whether this is in fact true appears uncertain.

The present study was undertaken in order to add in some measure to our present meagre knowledge of the natural history of cerebrovascular disease.

Material and Plan of Study

All patients who were admitted to the National Hospital for Nervous Diseases between January 1, 1950, and December 31, 1954, in whom a firm diagnosis of cerebrovascular disease was made and who were resident in Great Britain were the basis of the study. For the purpose of the study the term "cerebrovascular disease" includes haemorrhage, thrombosis, and diffuse arteriosclerosis involving either the cerebral hemispheres or the brain stem, and occlusion of the internal carotid or vertebral arteries. It does not include cerebral aneurysms or vascular malformations and cerebral emboli from causes such as endocarditis. Those in whom the diagnosis was in any way doubtful on the basis of the records were excluded. There were in all 305 such patients, 22 of whom died in hospital at the first admission, and these are not considered further, as the survey is concerned only with the long-term prognosis of the patients who survived.

A letter was sent to the practitioners of the 283 survivors asking if the patient was still alive, and, if so, whether he had experienced further cerebrovascular accidents. If the patient was dead the date and cause of death were requested. When information was not obtainable from the doctors, a letter was then sent to the patient. When neither of these sources provided the required information a search was made in the Registrar-General's register of deaths to see if the patient had died. By this means 251 (160 males and 91 females) of the 283 survivors were satisfactorily traced. Forty-five of the survivors who lived in the London area were personally examined at the time of follow-up. The results did not substantially alter the conclusions drawn from the wider postal survey with regard to such factors as the incidence of further accidents, hence this group will not receive further mention

TABLE I.—*Year of Admission to Hospital of the 251 Patients*

Year	Male	Female	Total
1950 ..	24	13	37
1951 ..	23	18	41
1952 ..	37	18	55
1953 ..	43	18	61
1954 ..	33	24	57
Total ..	160	91	251

The period of follow-up varied from four to nine years, the distribution of the cases among the years being shown in Table I.

Results

The clinical diagnoses in the 251 patients are shown in Table II. It should be pointed out that the figures have no meaning in terms of relative incidence: for instance, the small number of patients with haemorrhage simply reflects the infrequency of emergency admission as opposed to referral for diagnostic purposes. Of the 251 patients, only 17 were admitted within 48 hours of the onset of their illness. The word thrombosis in relation to the hemisphere is used to cover all non-haemorrhagic single focal disturbances in the cerebral hemispheres. This includes incidents which might be called thrombosis, spasm, insufficiency, or even embolism arising from an atherosclerotic plaque in the large arteries of the neck. It does not, however, include embolic infarction due to other causes such as rheumatic endocarditis. In this there may be no evidence that the cerebrovascular tree is inherently defective, and they have therefore been excluded entirely from the survey. The diffuse group includes patients with multifocal hemisphere lesions and those with arteriosclerotic dementia. Brain-stem thrombosis includes those patients in whom a diagnosis of basilar insufficiency might well be made. The diagnosis of an internal carotid thrombosis, complete or partial, was confirmed by arteriography in 21 cases, and in two was based on clinical evidence alone.

TABLE II.—*Initial Diagnoses of the 251 Patients*

		Males	Females	Total
Hemisphere	Haemorrhage ..	4	3	7
	Thrombosis ..	71	43	114
	Diffuse	47	30	77
Brain-stem thrombosis		21	9	30
Internal carotid thrombosis ..		17	6	23
Total		160	91	251

No attempt has been made to distinguish between transient ischaemic episodes and accidents resulting in permanent neurological deficit. Such a distinction would be of value, as the natural history of these two phenomena may differ widely. The method of inquiry available for this study did not, however, permit such distinctions to be made with sufficient accuracy to be reliable.

TABLE III.—*Prognosis for Life in Relation to Initial Diagnosis*

		Males		Females	
		Alive	Dead	Alive	Dead
Hemisphere	Haemorrhage	3	1	2	1
	Thrombosis	26	45 (64%)	23	20 (47%)
	Diffuse ..	11	36 (76%)	10	20 (66%)
Brain-stem thrombosis ..		11	10 (47%)	5	4 (44%)
Internal carotid thrombosis		8	9 (53%)	3	3 (50%)
Total		59	101 (63%)	43	48 (53%)

The prognosis for life in relation to the initial diagnosis is presented in Table III. The outstanding feature of this table is the high death rate among the patients with diffuse cerebrovascular disease, especially among the males. A second feature is that a thrombosis in the hemisphere carried a prognosis which was as bad as, if not worse than, a thrombosis of the brain stem. The time of death for males and females combined is

TABLE IV —*Time of Death in Years After Discharge from Hospital*

		Within 1	2	3	4	5	More Than 5	Time Unknown	Total
Hemisphere	Haemorrhage	1	—	1	—	—	—	—	2
	Thrombosis	4	11	15	9	14	8	4	65
	Diffuse ..	9	11	9	10	5	8	4	56
Brain-stem thrombosis ..		2	1	1	7	1	2	—	14
Internal carotid ..		2	1	2	2	1	2	2	12
Total		18	24	28	28	21	20	10	149

given in Table IV; it fails to show any peak period of mortality, but 119 of the 149 patients had died within five years of their accident.

The incidence of further cerebrovascular accidents among the patients who had survived is given for males and females combined in Table V. This shows a high incidence of non-recurrence in all diagnostic groups, 93% of the patients not having had a second attack. This is more remarkable in the group with brain-stem thrombosis, in which recurrent attacks are believed to characterize the progress of the disease.

TABLE V —*Incidence of Further Cerebrovascular Accidents in 102 Survivors*

		No Attacks	One Attack	More Than One Attack	Total
Hemisphere	Haemorrhage	3	—	—	5
	Thrombosis ..	45	2	2	49
	Diffuse ..	18	2	1	21
Brain-stem thrombosis ..		16	—	—	16
Internal carotid		11	—	—	11
Total		95	4	3	102

The incidence of hypertension and its relation to prognosis are given in Table VI for 248 patients. (In three instances there was no record of the blood pressure.) The blood pressure recorded was a single reading which had been taken as part of the general physical examination at the time of the patient's

TABLE VI.—*Comparison of Diastolic Blood Pressures in Survivors and Patients who Died*

	Blood Pressure	Alive	Dead	Total
Males	111 mm. Hg or above ..	13	37 (74%)	50
	110 .. .. .. below ..	46	62 (58%)	108
Females	111 .. .. .. above ..	11	20 (65%)	31
	110 .. .. .. below ..	31	28 (48%)	59
Total		101	147	248

admission. This is clearly a crude measure of the presence of hypertension, but it enables a rough distinction to be made between hypertensive and non-hypertensive patients. For the purpose of this study hypertension was defined as a diastolic pressure of 111 mm. Hg or above. Features worthy of comment are (1) that there were twice as many patients without hypertension as with; (2) that there was no significant difference in the incidence of non-hypertensive vascular disease in the men and women; and (3) that the mortality was higher in the hypertensive group.

TABLE VII.—*Prognosis for Life in Relation to Age at Time of Admission to Hospital*

Age	Alive	Dead	Total
30–39	1	3	4
40–49	24	15 (38%)	39
50–59	43	42 (49%)	85
60–69	24	69 (74%)	93
70–79	9	20 (69%)	29
80	1	—	1
Total ..	102	149	251

The prognosis in relation to the age of the patients at the time of their admission to the hospital is shown in Table VII, which shows a much higher mortality rate in the patients who were over 60.

The cause of death is shown in Table VIII.

TABLE VIII.—*Causes of Death in Each Diagnostic Group*

		Cerebrovascular	Cardiac	Other	Unknown	Total
Hemisphere	Haemorrhage	1	—	—	1	2
	Thrombosis	29	12	16	8	65
	Diffuse ..	24	12	14	6	56
Brain-stem thrombosis		8	3	3	—	14
Internal carotid ..		7	2	1	2	12
Total ..		69	29	34	17	149

Discussion

In retrospective studies there are many defects which cannot be avoided, as the type of patient, their mode of admission, and the records available are predetermined. This does not render a retrospective study without value, but it is essential to be fully aware of the limitations of a particular study in order to avoid unjustified conclusions. The present material is in no way representative of acute cerebrovascular disease, for, as has already been pointed out, only 17 of the 251 patients were admitted within 48 hours of the onset of their illness. Nor is it an adequate geographical sample, as the patients came from all parts of the country.

The series contained a higher proportion of diagnostic problems than might be usual in a group of patients suffering from cerebrovascular disease. On the other hand, the group had been subjected to a more careful clinical scrutiny than is commonly given to cerebrovascular patients, which made the classification of the lesion according to its site and pathology more certain. Hence, though no conclusions can be drawn with regard to the many aspects of acute cerebrovascular accidents, the material provides a group of carefully diagnosed cases in which the long-term prognosis of various types of cerebrovascular lesion can be studied.

The most striking feature was undoubtedly the high mortality associated with diffuse cerebrovascular disease of the hemisphere, more especially in the males. These patients presented clinically either with dementia or with a history of multiple and transient strokes. They tended to die sooner rather than later, 21 of the 36 deaths occurring within three years in the males. The commonest cause of death in this group was a cerebrovascular accident. There was considerable evidence from practitioners and relatives that the condition of the patients had deteriorated before death, many becoming severely demented, incontinent, and completely dependent on others.

The second most lethal condition in this series was a thrombotic incident involving the cerebral hemisphere, 64% of the males and 47% of the females having died at the time of the follow-up, a cerebrovascular accident again being far and away the commonest cause of death. This is surprising, as it is commonly believed that a thrombosis may carry a good prognosis. That it may do cannot be denied, as examples of patients surviving one or even two decades after a thrombosis are well recognized; but, overall, the prognosis is not good.

The findings with regard to brain-stem thrombosis were the most surprising. This condition is generally regarded as carrying a poor prognosis, the tendency being for the patient to have recurrent attacks until he succumbs. The outlook is believed to be much inferior to that of a hemisphere thrombosis. The present figures belie this view, the prognosis for both males and females being better for those with a brain-stem thrombosis than for those with a hemisphere thrombosis. Currier *et al.* (1958) had noted the same point in their study of thrombosis of the posterior inferior cerebellar artery, and said, "They live an average of more than five years, a survival rate that is probably comparable to that of all 'cerebral' thromboses in general, and not to the short span that is usually thought to be associated with involvement of the vertebral-basilar system." It seems, therefore, that there is need for revision of present views on the relative long-term prognosis for the various types of cerebrovascular lesion.

The mortality of internal carotid thrombosis was high, 52% of the patients having died at the time of follow-up. It is as yet too early to know whether the long-term outlook will be improved by surgery as now carried out (Edwards and Rob, 1956; Rob and Wheeler, 1957).

The commonest cause of death in all diagnostic groups was, as might be expected, a cerebrovascular accident, this being twice as common as cardiovascular causes, which were by no means infrequent.

The fact that 93% of survivors had no further attacks up to the time of follow-up is a startling one, but must be interpreted with considerable caution. It may be that the patients who died had recurrent attacks, for Pincock (1957) has noted that recurrence carries a high mortality. This is supported by the present observation that the commonest cause of death in all groups was a cerebrovascular accident. Those who have no further incidents may be the ones whose prognosis is good and who will survive. It would be of great value to know the incidence of further cerebrovascular accidents in those who died, but a retrospective study does not provide information of this kind with sufficient reliability. The information would be dependent on practitioners remembering details of illness in patients who had died anything from four to eight years previously. This question can be settled only by a prospective study, which we are at present undertaking.

These observations raise important issues with regard to the assessment of methods of treatment. If the non-lethal recurrence rate was as low in those who died as in the survivors then the outlook for cerebrovascular disease is better than is generally believed. If, on the other hand, the recurrence rate is high in those who died, it seems reasonable to postulate that for reasons unknown two distinct groups emerge from those who have a single cerebrovascular accident. One group comprises those where further progress is punctuated by recurring attacks leading to early death; patients in the other group have few further accidents and survive many years. Thus the method of assessing the value of a treatment by using a patient as his own control and comparing periods before and after the initiation of treatment in a condition in which we are so uncertain of the natural history is open to serious fallacies.

The relatively high incidence of non-hypertensive vascular disease in the present series cannot be regarded as of significance, because a patient with cerebral symptoms who is found to be hypertensive is more likely to be referred to a general physician than is a non-hypertensive patient. The fact that the mortality among those with hypertension is greater than among the non-hypertensives is what might be expected.

Attention has already been called to the defects of retrospective studies, defects from which the present study is not free. It has, however, some value; firstly, in raising the suspicion that some of our opinions about the natural history of cerebrovascular disease are without firm foundation: for example, the worse prognosis given to vascular disease of the brain stem as compared with that of the cerebral hemispheres is not justified by the present data. Secondly, the low incidence of recurrent accidents in the survivors is an unexpected finding. Beyond this it is not possible to draw further conclusions, but the need for prospective studies of the natural history of cerebrovascular disease and for properly controlled clinical trials in the assessment of methods of treatment is abundantly clear.

Summary

A series of 251 patients diagnosed as suffering from cerebrovascular disease have been surveyed after periods of four to nine years.

The mortality, incidence of further cerebrovascular accidents, cause of death, and prognosis in relation to age and blood pressure have been ascertained.

Although some information has been provided about the natural history of cerebrovascular disease, the detailed knowledge required for a clear assessment of methods of treatment can be provided only by carefully planned prospective studies.

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By the end of April over 1 in 4 in the 15–26 age group in Great Britain had volunteered for vaccination against polio, compared with only 1 in 12 two months earlier. The total rose from 517,000 to 1,586,000—representing an acceptance rate of just over 25%—and of those 600,000 have had two doses and a further 700,000 one dose. Announcing these figures on June 3 the Ministry of Health stated that at the same date over 9,760,000 in the priority groups had received injections, over 8,600,000 having received two and over 3,100,000 three. The acceptance rate for children up to 15 years of age had risen to nearly 69% (compared with 63.5% at the end of February). A further 54,000 expectant mothers volunteered in March and April, bringing the total to 272,000. A Ministry of Health official commented: "The jump in the number of young people who have been vaccinated is probably even bigger than the official figures disclose at the moment, because it is thought that they do not yet include all of the many hundreds of thousands who were vaccinated by their family doctors during the big rush which started in April."

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SINGAPORE TRIAL OF LIVE POLIOMYELITIS VACCINE

Inactivated (Salk) poliomyelitis vaccine as at present used takes several weeks to confer protection and is therefore unlikely to be effective as an emergency measure once an epidemic has started. On the other hand, a living attenuated vaccine, by interfering with infection by "wild" virulent virus, might protect quickly enough to be used to control an epidemic. Moreover, there is some evidence that immediate interference of one virus with another is less type specific than the lasting immunity which develops more slowly. During the past year Professor J. H. Hale and his colleagues in Singapore have tested this idea by feeding children with Sabin's type 2 vaccine during an epidemic of paralytic poliomyelitis due to type 1 virus. Their preliminary report[1] was published in last week's *Journal*. The assessment of the trial, the importance of which has already been referred to by Dr. Sabin,[2] deserves the closest possible attention, because there are unlikely to be many equally clear or well-recorded pieces of evidence on which to guide future policy.

The Singapore epidemic started in August, 1958. The decision to feed Sabin's type 2 vaccine was made eleven weeks after the appearance of the first cases. Altogether 198,965 children received the vaccine by mouth, most of them during the seven weeks after this decision. Among these vaccinated children there occurred sixteen cases of paralytic poliomyelitis, but ten of these evidently received their vaccine while they were incubating the disease, so that there were only six who may be said to have developed the disease in spite of vaccination. These figures are compared with 179 cases among 300,000 children who were not vaccinated. The total number of cases in the epidemic was 415. If these figures are taken at their face value, which is all that can be done until the complete report appears, it is evident that vaccination with living type 2 vaccine gave substantial protection against the epidemic type 1 strain.

Professor Hale and his colleagues are cautious about the numerical interpretation of their results. Statisticians may well feel that they need more information about the timing of events and the composition of the vaccinated and unvaccinated groups. Moreover, as the authors point out, many of the children included in the unvaccinated group probably became infected with the vaccine strain by contact with vaccinated children, for there was good evidence that such spread occurred. The effect of the vaccine on the epidemic as a whole is hard to assess, because the peak had probably been reached before vaccination was complete. Since the duration of the protection given is not known, it is impossible to judge what might have happened had the vaccine been given earlier.

As important as knowledge about the efficacy of the vaccine is knowledge about its safety. The evidence of the Singapore trial on this point is more difficult to assess. One reason why type 2 vaccine was chosen was that no paralytic case due to type 2 virus had been reported in Singapore itself since June, 1956. Antibody surveys made in April, 1956, and again before vaccination began in 1958 suggested that type 2 virus was active in the Singapore population, but the stools of 248 healthy children examined just before the vaccination campaign yielded no type 2 virus, although seven strains of type 1 virus were recovered from them. Strains of type 2 virus recovered after the vaccine had been administered, whether they came from either vaccinated or unvaccinated children, were assumed to be the vaccine strain. Twenty-seven such strains were tested by intraspinal and intracerebral inoculation of monkeys: none gave evidence of high monkey virulence, although Professor Hale and his colleagues state that their results, like those of others, revealed "some strains with slight increase in pathogenicity." During the course of the trial only one case of paralytic poliomyelitis yielded a type 2 virus: this was a child 4 years of age who fell ill in the twentieth week of the epidemic and nine weeks after the start of vaccinations. No other cases due to type 2 virus had been found in Singapore since June, 1956, but type 2 cases were known to have occurred recently in the neighbouring town of Johore Bahru, so that this single Singapore case may have been due to imported virus and not to the vaccine strain. The vaccine apparently proved safe in this trial to the vaccinated children and, with the possible exception of the single case referred to above (for the child concerned was presumably not vaccinated), to those infected with the vaccine strain from them. The evidence of safety to children infected by spread from the vaccinated during the months which followed will have to be judged on the adequacy of the

[1] Hale, J. H., Doraisingham, M., Kanagaratnam, K., Leong, K. W., and Monteiro, E. S., *Brit. med. J.*, 1959, I, 1541.
[2] Sabin, A. B., ibid., 1959, I, 663.

surveillance arrangements, details of which are promised in the full report. It is to be hoped that the future behaviour of type 2 virus in Singapore will be watched as closely as possible, because so little is still known about the conditions in which "wild" avirulent strains become virulent, if in fact they do so—and it seems that they must—that there cannot be complete certainty that vaccine strains would not behave in the same way given the same, unknown, circumstances.

Professor Hale and his colleagues are to be warmly congratulated on the skill and vigour with which they have seized a rare opportunity. Their reports will be scrutinized with the most minute attention because they provide the best evidence so far available on the behaviour of living attenuated vaccine used on a large scale in circumstances such that careful and reliable recording of subsequent events is possible. The value of trials of this kind rests on the quality of the surveillance. A trial can give reliable information only if very thorough observation of the whole population involved, whether vaccinated or not, is possible; otherwise it is likely to do more harm than good by obscuring what really happens and confusing both informed and uninformed opinion.

The Singapore trial inevitably raises the question whether in the event of an epidemic of paralytic poliomyelitis in a country such as the United Kingdom living attenuated vaccine should be used as an emergency measure. This would be a very difficult question to answer in the light of the scanty knowledge we yet have about the safety, and the efficacy in the field, of living vaccines. It is earnestly to be hoped that the question may never arise, and that vaccination with inactivated Salk vaccines may have been pursued with sufficient thoroughness in time to prevent future epidemics from ever developing.

A NEW HYPNOTIC

The properties of the substance methyl orthotolyl quinazolone, known as TR 495, have recently been described by A. Ravina.[1] It is not a barbiturate, but is nevertheless a hypnotic said to have an activity greater than that of phenobarbitone and of butobarbitone. The hypnotic action can be demonstrated in the mouse, the guinea-pig, and the rabbit, and even in Siamese fighting-fish. In a concentration of 10 μg./ml. these swim slowly and calmly in perfect balance, and do not display their normal aggressiveness. In man the hypnotic properties have been determined in 100 patients who were seriously ill, many of them having malignant tumours. In 20 of these the results were excellent, patients getting a long night's sleep who were otherwise unable to do so. In 34 cases the results were better than those with other hypnotics, among which was counted chlorpromazine. In 28 cases the results were moderate, the period of sleep not being very long, and in 12 cases they were not so good as the results with other hypnotics. In 6 cases the results were bad, for the patients only became confused. The author considers that the substance has value because the high proportion of good effects were obtained in patients who had taken the usual hypnotics with little result. Side-effects were rare. Two complained of indigestion, nausea, and a burning sensation in the stomach. No changes in the blood were detected, and the number of platelets in a woman suffering from a toxic purpura was not diminished.

[1] Ravina, A., *Presse méd.*, 1959, **67**, 491.

BIRTHDAY HONOURS

The baronetcy conferred on Professor Robert Platt is a welcome recognition of his presidency of the Royal College of Physicians. Fellows of the College will receive this news with acclamation. Since he was first elected President in 1957 Professor Platt has made the influence of the College more and more felt in medical research and education and has played an active part in encouraging the work of the College of General Practitioners. In all this he has shown a remarkable capacity for securing the co-operation of groups with diverse interests. As professor of medicine in the University of Manchester, a post to which he was appointed in 1945 when aged 45, Professor Platt has provided a great stimulus to clinical research. His own work, especially on kidney disease, has brought him an international reputation. His Lumleian lectures on "Structural and Functional Adaptation in Renal Failure" were published in the *British Medical Journal* of June 21 and June 28, 1952.

The advancement of Dr. Wilfrid Sheldon to K.C.V.O. honours the work that this distinguished paediatrician has done for the Royal Family. He holds appointments at King's College Hospital and the Hospital for Sick Children, Great Ormond Street. Also made K.C.V.O. is Sir Archibald Gray. Prominent both as a dermatologist and as a university administrator, especially in his endeavours to improve medical education, Gray has combined his duties in the skin department at University College Hospital with membership of many influential committees, including the Goodenough committee on the organization of medical schools. He has also played a key part as dean of the medical school at U.C.H. and of the medical faculty in London University. The K.B.E. is awarded to Air Vice-Marshal F. W. P. Dixon, an Australian who qualified at Melbourne and has made a distinguished career for himself as a surgeon in the R.A.F.

There are three Knights Bachelor. Professor Dugald Baird is well known for his many and continuing researches at Aberdeen to make child-bearing safer for mother and baby. Professor Aubrey Lewis, an Australian who qualified at Adelaide, has directed the professorial unit at the Maudsley Hospital, London, since 1946. And Mr. Alexander Gillies is consulting surgeon to Wellington Hospital in New Zealand.

Drug Treatment of Disease

PRINCIPLES OF MODERN STEROID THERAPY: PART II

BY

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PHARMACOLOGICAL EFFECTS

The relatively simple steroid desoxycorticosterone exerts a profound effect on excretion of sodium and of potassium, especially in subjects with inadequate adrenal function. Under its influence sodium is strongly retained and potassium excreted at an increased rate. This effect is of the greatest value in the treatment of Addison's disease, but it is very much less evident in subjects with intact adrenals. Desoxycorticosterone has, however, only very slight actions in other ways. It has, for instance, little or no effect on rheumatoid arthritis. Most of the adrenal steroids possess in varying degree this tendency to cause sodium retention and potassium excretion. Although the former is often mild with cortisone or hydrocortisone, yet it may be enough to produce oedema, and is clearly an undesirable feature in some subjects—such, for instance, as those with congestive cardiac failure or a tendency to oedema from other causes.

The true adrenal hormones and their analogues have several other effects which are not shown by desoxycorticosterone. They promote powerfully the deposition of glycogen in the liver, and this so-called glycogen effect has been used for their assay. Another interesting phenomenon shown by most of these steroids is that when their concentration in the blood stream rises the eosinophil cells of the circulating blood promptly disappear. Both cortisone and hydrocortisone are especially potent in these effects. An increased activity of the adrenal cortex in producing hydrocortisone is thus to be detected by a fall nearly to zero of the eosinophils in the blood stream. This may be expected as a usual reaction resulting from a normal adrenal response to stress, and persistence of the eosinophils in any severe stressful situation such as after an operation or during shock is suggestive of failure of adrenal function. The circulating lymphocytes are also reduced by these steroids, but this effect is of much less clinical value.

Another effect which can have serious clinical import is that most of these steroids provoke a negative balance of calcium, largely owing to increased faecal excretion. With this there is also abnormal loss of phosphate. Both these are referable to a loss of mineral from the bony skeleton, and this, if prolonged, may lead to osteoporosis and collapse of one or more vertebrae. The body usually loses nitrogen also, some of the loss coming no doubt from the bones, but much from the tissues and muscles.

On carbohydrate metabolism the main effect of these steroids is a tendency to produce a diabetic type of sugar curve, but this is rarely of serious clinical import. Deposition of glycogen in the liver is strongly stimulated, an action which roughly parallels the antirheumatic activity of the hormones.

Therapeutic Actions

Though knowledge of these actions is important, since they account for many of the clinical side-effects and complications, none of them explain the important therapeutic effects for which the adrenal steroids are now so widely given. It is indeed fair to admit that so far no adequate explanation of the mode of therapeutic action of these steroids has been offered. What is evident is that they reduce very strongly the manifestations of inflammatory reactions, the hyperaemia, the oedema, the swelling, the fibroblastic activity and proliferation, and often the pain. Many of the benefits of the steroids are directly referable to these so-called anti-inflammatory effects—in topical skin therapy, in ulcerative colitis, and in asthma, for instance. It is a curious fact that the types of inflammation most readily inhibited in this way are those usually regarded as of unknown aetiology. Allergic reactions are similarly benefited, however, in equally dramatic manner. Whether or not this inhibition of inflammation is of benefit in the individual case will depend on many complex factors. The clearly allergic cases and those of uncertain aetiology generally receive benefit. But if the cause of the disease is bacterial the inhibition of the normal inflammatory resistance to bacterial invasion can quickly have disastrous consequences. It is thus essential for a full diagnosis to be made before steroid therapy is started.

In addition to having such local effects steroids inhibit some of the general manifestations of disease. Thus fever is usually lowered considerably, often to normal; the sedimentation rate, if raised, will usually be reduced; and general malaise, so common in many diseases, may be replaced by a sense of well-being and even euphoria. It is worth bearing in mind that all these changes are non-specific effects of the adrenal steroids and by no means indicate necessarily that the disease is being favourably influenced. Indeed, their occurrence in a patient when given steroids can all too easily lull the anxious physician into a false belief that he is doing good rather than harm.

Of the many effects which these steroids are known to produce, some are undesirable and determine the complications—such, for instance, as the tendency to sodium retention and loss of calcium, and others seem to be more closely related to the beneficial therapeutic action on disease.

None of the pharmacological actions adequately explain the therapeutic benefit, and this is perhaps best measured for clinical purposes by the so-called antirheumatic effect, since selected cases of rheumatoid arthritis can permit a fairly sensitive comparison of the potency of one steroid with another. The main concern of the synthetic chemist has been to reduce the undesirable sodium-retaining action while at the same time enhancing the antirheumatic effect, so that smaller doses are needed. Reduction of dosage is particularly desirable because of a marked tendency of these steroids to cause gastric irritation and even formation of gastric ulcer when given by mouth. It is hoped that more potent steroids in smaller dose will have a less irritant effect on the stomach, and there is a little evidence to support this view.

Chemical Modifications

With these points in mind the effects of the various chemical modifications to the parent molecule may be briefly reviewed.

The slightly lower potency of cortisone compared with hydrocortisone is probably due in part to less efficient absorption and in part to the need for conversion to hydrocortisone in the body.

The introduction of the second double bond in ring A as in prednisolone increases by about four times the antirheumatic activity, but hardly influences the effect on the electrolytes. However, since the active dose is reduced to about a quarter, the effect of therapeutic dose on retention of sodium is proportionately reduced.

Attachment of fluorine to 9 carbon greatly increases the sodium-retaining action, more indeed than it increases the antirheumatic effect, so that this steroid is particularly useful for control of electrolytes in substitution therapy.

Attachment of a methyl group at carbon 2 still further increases electrolyte potency, but very curiously a methyl or hydroxyl group at carbon 16 seems to abolish almost completely the electrolyte activity of the steroid. The 16 hydroxyl group is present in triamcinolone, of recent introduction, but the 16 methyl group impairs a six times higher antirheumatic potency to the steroid, with corresponding general advantages, as in dexamethasone.

The actions of some of the clinically important steroid variants are compared roughly in the Table. Many of the figures given there are very approximate, though the relative dosages in the final column are a clinically useful comparison. At present the latest steroid to be introduced, Δ^1-9α-fluoro-16-methylhydrocortisone, offers the best clinical prospects in that it has very high antirheumatic activity with a negligible sodium-retaining effect, but clinical experience with it is still very small.

Steroid	Glycogen Deposition	Electrolyte Excretion	Eosinopenia	Antirheumatic	Granuloma Inhibition	Relative Dosage
Hydrocortisone (F) ..	1	1	1	1	1	100
Cortisone (E) ..	0·8	0·8	0·8	0·8	1	130
Prednisolone (Δ^1F) ..	4	1	3	4	20	25
Prednisone (Δ^1E) ..	3	1	3	3	16	30
Aldosterone	0·3	50	—	0	0	—
9α-Fluorohydrocortisone (9α-FF)	20	50	20	20	20	5
Δ^1-9α-Fluorohydrocortisone	20	50	20	20	—	3
2-Methyl-9α-fluorohydrocortisone	10	200	2	—	40	—
Δ^1-Methylhydrocortisone	10	—	3	4	—	20
Triamcinolone (Δ^1-9α-fluoro-16-hydroxy-F)	30	Nil	3	4	10	25
Dexamethasone (Δ^1-9α-fluoro-16-methyl-F) ..	17	,,	15	28	190	4

REPLACEMENT THERAPY

As soon as effective steroid therapy is instituted the adrenal cortex is promptly inhibited, usually within 24 hours, so that replacement therapy is in a sense the only form of therapy which one can apply. This means in effect that, once the physician has started therapy, he alone becomes responsible for the maintenance of steroid metabolism in that patient. If the external supplies are withheld either by accident or design, the inhibited adrenal cortex may be unable for a day or two to revive sufficiently to resume its normal production of hydrocortisone. Seriously adverse effects, even including fatal adrenal crisis, can occur during this interim period. The initiation of steroid therapy thus imposes a heavy responsibility on the physician.

Therapeutic policy can be divided in general into two types: (1) the replacement of normal adrenal cortical function, lacking because of an inactive adrenal; (2) alternatively the deliberate raising of the level of steroid concentration above normal levels in body fluids, which is the aim in most forms of systemic steroid therapy.

Adrenal Behaviour

In simple replacement, then, the aim is to imitate natural adrenal behaviour. But two aspects of activity need to be considered—the electrolyte-controlling function normally controlled by aldosterone, and the hydrocortisone-producing function. In *Addison's disease* and after *total adrenalectomy* both these are lost, but in hypopituitarism only production of hydrocortisone needs to be replaced, since formation of aldosterone is not dependent on stimulation by the pituitary.

The normal human adrenal secretes ·12.5–25 mg. hydrocortisone daily, and this is found clinically to be the quantity required for minimum maintenance. The sodium-retaining effect of this small dose is often not sufficient to replace the lost aldosterone, and some steroid with a more potent salt-retaining action is usually needed. Desoxycorticosterone as trimethyl acetate injected once a month is usually sufficient, in a dosage of 37 to 50 mg., or the potent steroid 9α-fluorohydrocortisone may be given in doses of 0.5 to 1 mg. daily by mouth. Signs of overdosage of the sodium-retaining steroid must be looked for, especially oedema, raised jugular venous pressure, and increased heart size at *x*-ray. While the sodium-retaining steroid can usually be maintained at a steady level, the patient's needs for hydrocortisone may vary considerably. A very active life may increase them appreciably, but any stress such as infection, trauma, or operation calls for much bigger amounts; in such circumstances the dose of cortisone acetate should be raised to 100 or 200 mg. daily temporarily.

So important is it to increase the dosage of steroid during such stresses that all patients on replacement therapy should be clearly instructed about the need; all should have steroid tablets constantly available; and all should carry on their person a statement that they are receiving steroids and an indication of the dose, so that, should an accident result in unconsciousness, their steroid intake will not be interrupted.

It is because the need for hydrocortisone and the electrolyte-controlling steroid do vary a great deal independently of one another that it is usually desirable still to administer both steroids to the patient with Addison's disease. In theory one steroid should exist with the right proportions of the two actions for normal needs, and 9α-fluorohydrocortisone probably approaches closest to this. But this steroid, on which the patient with quiescent Addison's disease can be maintained, is insufficient by itself to meet the demands of stress without also causing retention of sodium.

Resistance to Infection

The view that steroid therapy tends to reduce the body's resistance to bacterial invasion is well fou[illegible] and the problem frequently arises of patie[illegible] bacterial disease who need replacem[illegible] Addison's disease with active tubercle eith[illegible]

of adrenal glands is perhaps the best example. In such circumstances maintenance therapy, which aims at merely replacing normal adrenal production, is likely to improve rather than reduce the patient's resistance. It is excessive dosages such as may be needed for therapy of some diseases which reduce bacterial resistance.

Pregnancy occasionally occurs in patients with Addison's disease; it constitutes a mild stress. During most of its course the patient can usually receive a daily dose of 25 to 37.5 mg. cortisone acetate daily. Labour, either natural or by caesarean section, is a more severe stress, and daily doses of 100 to 200 mg. of cortisone acetate are needed to cover this period.

In *hypopituitarism* the problem is usually simpler. Production of hydrocortisone is lost, but in contrast to Addison's disease the production of aldosterone is not appreciably impaired. The need is for the replacement of the former, but additional control of electrolytes is not needed. Oral cortisone acetate in a dosage of 12.5 to 25 mg. daily is all the adrenal steroid replacement needed. In practice, however, it is frequently found that testosterone gives the patient more subjective benefit than does cortisone. It is important and sometimes difficult to persuade such subjects that they need the additional cortisone.

In *total adrenalectomy* the conditions are essentially those of Addison's disease but aggravated by the persistence of the disease—carcinoma or severe hypertension—for which the operation was performed. Although many patients with adrenalectomy have been maintained on cortisone alone without recourse to electrolyte-controlling steroids, this is an essentially precarious regime, and it is desirable to include in the therapy a small quantity of either desoxycorticosterone trimethyl acetate as a once-monthly injection or a small daily supplement of the very potent electrolyte-controlling steroid 9α-fluorohydrocortisone. This should go far to ward off the risks of adrenal crises developing in such subjects.

Medical Emergencies

The condition of acute *adrenal crisis* is one of the important medical emergencies calling for prompt action. Such crises may be divided usefully into several types. Sudden shock-like collapse occurring in subjects with known adrenal inadequacy, whether due to disease of the glands, to their surgical excision, or to recent steroid therapy, is not especially difficult to suspect, since such subjects are known to be at risk. A further group comprises cases of acute adrenal failure in a previously normal gland. The Friderichsen–Waterhouse syndrome is the best-known example of this, but it may occur occasionally under a wide variety of other clinical situations. In both these types the urgent need is for large volumes of saline and for prompt supplies of hydrocortisone. In such circumstances the oral route is often uncertain and impracticable, and absorption from intramuscular sites too slow owing to the poor circulation, so that the only safe route is the intravenous. A dose of 100 mg. of any of the intravenous preparations of hydrocortisone added to the saline drip is usually sufficient to correct the deficiency. The third group consists of those problem cases of shock, often post-operative, in which, though adrenal failure has not previously been suspected, it may be a factor in the crisis, yet there is no time to make tests to find out. Such problematic situations are not infrequent; many hypotensive crises which fail to respond to noradrenaline will fall in this category. When one is suspected, intravenous hydrocortisone should be promptly given. It may be life-saving, but if no benefit results it will have done no harm, and adrenal failure as a major factor in the collapse will have been excluded.

There remains one other type of steroid replacement therapy to consider, that of *congenital adrenal hyperplasia*. In this disorder there is a primary inability of the adrenal cortex to synthesize hydrocortisone and sometimes also there are defects of electrolyte control. The steroid metabolism of such patients, whether children or adults, can be restored almost to normal by supplying cortisone. Though this is fairly effective when given orally, it is more so when given as an intramuscular injection, for such a depot provides a more regular supply of the hormone. When the balance of electrolytes is disturbed small doses of desoxycorticosterone or of 9α-fluorohydrocortisone may be needed in addition.

In conclusion, it is worth emphasizing that the initiation of systemic steroid therapy makes the physician completely responsible for the patient's hydrocortisone metabolism. Consequently, failure to follow the basic principles or to recognize small warning signs of impending complications may seriously harm the patient. For these are potent drugs having an action on fundamental processes in the body's reaction to disease which are as yet little understood. Therapy, to be successful, must be preceded by accurate clinical diagnosis and accompanied by close attention to the diverse clinical effects on the individual patient.

Any Questions?

Gout and Disk Lesions

Q.—*Is there any relationship between gout and disk lesions?*

A.—There is no relationship between gout and disk lesions. Gout is a metabolic abnormality characterized by acute attacks of pain in peripheral joints, usually starting in the big toe, and by a high level of uric acid in the serum. A disk lesion is a mechanical condition in which a prolapsed intervertebral cartilage, usually in the lumbar or cervical region, presses either on the posterior ligament or a posterior nerve root causing pain which may radiate down the sciatic or a lower cervical root distribution. The treatment of each condition is quite different.

Sewage Purification

Q.—*To what extent are pathogenic organisms in sewage rendered innocuous by treatment in settlement tanks, percolating filters, humus tanks, etc.?*

A.—Pathogenic organisms are not affected to any significant extent by the ordinary processes of sewage purification. Such purification aims only at providing an effluent of a satisfactory chemical standard, and any reduction which has taken place in the pathogenic bacteria is due almost entirely to the passage of time and not to any factor in the so-called purification system. It is becoming increasingly the custom to chlorinate effluent from sewage-disposal plants, and, of course, when this is done the bacterial standard is greatly improved, but such effluent should never be considered as fit for drinking purposes.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Fungus in Swimming-baths

SIR,—Since 1956 sampling tests for dermatophytes have been made intermittently at public swimming-baths in Battersea and Wandsworth. When fungus was recovered from the floors it was almost invariably the *interdigitale* type of *Trichophyton mentagrophytes*, and in this respect the findings tally with those of Miss Mary P. English and Dr. Mary D. Gibson (*Journal*, June 6, p. 1446). On 2 of 75 occasions, however, *T. rubrum* was isolated.

Serial tests were made before and after treatment of the floors and cubicles with non-toxic solutions of chloride and hypochlorite preparations, copper sulphate, thymol, and cetrimide. Dr. Jacqueline Walker, of the School of Hygiene and Tropical Medicine, London, has demonstrated that both thymol and cetrimide are effective *in vitro* against cultures of *T. interdigitale*, *T. rubrum*, and *Epidermophyton floccosum*, but so far no conclusive evidence has been obtained that the use of any chemical preparation on a large scale is effective in eradicating fungus from the baths.

More research is required on the use of chemical applications combined with mechanical measures such as cleaning and sluicing. Perhaps cetrimide treatment merits further attention.—I am, etc.,

Public Health Department, Wandsworth, S.W.18. A. GARLAND.

Griseofulvin in Ringworm

SIR,—Investigations by workers such as Martin[1] on laboratory animals, and Gentles[2] on large beasts such as cattle, demonstrated the remarkable effect of oral griseofulvin on certain cutaneous fungus infections. This work has been fully confirmed in humans by Williams *et al.*[3] in London, by Blank *et al.*,[4] and by Pardo-Castello in Cuba. It appears that a dosage of 1 g. daily is adequate in most cases of dermatophytosis and tinea unguium, though the drug must be taken regularly for several months. In this concentration toxic reactions do occur, but not nearly so frequently as with a higher dose such as 2 g. daily.

However, I believe that this higher dosage may be necessary in some fungus infections. So far, I have treated only five patients with severe kerion celsi caused by cattle ringworm—of these, four were given 2 g. daily for 14 days with dramatic response, while the fifth showed little or no improvement after a fortnight on 1 g. daily but cleared readily when the dose was increased to 2 g. daily. In such cases, only a short course of treatment is required, so that the risks of serious toxic effects are slight.

Though Martin[1] observed that two laboratory attendants who were accidentally infected with *Trichophyton mentagrophytes* responded well to the local application of griseofulvin, it should be noted that griseofulvin ointment 1%, used in a controlled series of cases of tinea pedis, was no more effective than two well-known fungicidal ointments.[5]

Acknowledgment is made to Dr. Mungavin and Dr. Dobbie, of Imperial Chemical Industries Ltd., for generous supplies of griseofulvin tablets and ointment.

—I am, etc.,

Royal Infirmary, Edinburgh. G. A. GRANT PETERKIN.

REFERENCES

1. Martin, A. R., unpublished data, 1956.
2. Gentles, J. C., *Nature (Lond.)*, 1958, **182**, 476.
3. Williams, D. I., Marten, R. H., and Sarkany, I., *Lancet*, 1958, **2**, 1212.
4. Blank, H., and Roth, F. J., jun., *A.M.A. Arch. Derm.*, 1959, **79**, 259.
5. Peterkin, G. A. G., and Brewster, G., *Practitioner*, 1958, **180**, 543.

Hyperthyroidism and Periodic Paralysis

SIR,—Having recently seen a similar case, I was extremely interested in the article by Drs. N. Anderssen and K. Wigmostad on hyperthyroidism and periodic paralysis (*Journal*, May 30, p. 1389).

My patient is a 28-year-old officer in the Royal Navy, who, while under out-patient observation for possible thyrotoxicosis, developed sudden weakness of the legs during a warm night on May 20 this year. When I saw him the following morning motor power had returned though deep reflexes were sluggish. There was a marked regular tachycardia and fine tremor of the outstretched fingers. A slight, but definite, smooth enlargement of the thyroid gland has since developed and he is shortly to be admitted to a hospital in London for radio-iodine uptake tests.

Following the attack of nocturnal weakness I put him on treatment with phenobarbitone, and also gave him a bottle of mist. pot. cit., somewhat empirically, as prophylaxis against further attacks. He has not had any, though muscle fatigue is prominent on walking in hot weather. Neostigmine has not been tried. On direct questioning he has admitted that he had a previous episode of lower limb weakness while out sailing on a warm day about a week before his nocturnal attack.

It is interesting that both in this case and that of Drs. Anderssen and Wigmostad the onset of muscular weakness took place in early summer, when the warmer weather can be expected to precipitate a latent thyrotoxicosis.—I am, etc.,

R.N. Sick Quarters, Ipswich. R. A. L. AGNEW.

Muscle Pain after Short-acting Relaxants

SIR,—I am greatly interested in the paper by Dr. R. A. L. Leatherdale and his colleagues (*Journal*, April 4, p. 904) on the incidence of "muscle pain" after short-acting relaxants, particularly as he refers to my suggestion that they might be due to the products of deterioration.

He is satisfied that there is no difference in the incidence whether the chloride or bromide is used, which clears up one point—it is to be regretted that he used normal saline to dissolve the suxamethonium bromide, as he is thereby administering more chloride than is contained in suxamethonium chloride, which may cloud the issue.

The incidence in my hands is still considerably less than the figures obtained by Dr. Leatherdale *et al.*, and I am very interested to know why. Strangely enough, last week I had a case in a young female, who had previously had the same anaesthetic for the same operation but without any muscle pains, the only difference being that on the first occasion, in January, she was premedicated with "omnopon" 1/3 gr. (22 mg.), hyoscine 1/150 gr. (0.43 mg.), and was induced with 0.3 g. hexobarbitone, whereas this time she had 1/6 gr. (11 mg.) omnopon, 1/100 gr. (0.65 mg.) atropine, and 20 mg. levopromazine and required only 0.2 g. hexobarbitone for induction. On both occasions she was up and about the ward within four hours of the operation.

So far none of us knows why muscle pains occur at all, or why they do not occur all the time. I use no other relaxant—except for neonates—old, young, weak, strong, fat, thin, they all get it, and I very rarely have any complaint about muscle pain. Never have I seen it in a child, and they ambulate quickly enough in all truth; and, as regards the argument that females get back to work earlier than males, in this country the men get back to work as quickly as they can, but I would agree that it is more common in the female.

I do not think that the incidence is related to the quantity of the barbiturate used in the induction, but I do think it may be related to the circulation time—if the barbiturate is not well distributed by the time the relaxant is given, pain may occur—do we know what the incidence is when it is given without a barbiturate?

I wonder what the incidence is with workers who, like myself, use a short-acting relaxant exclusively—there is no doubt that familiarity with a particular drug lessens the incidence of complications. For example, one of the complications cited in the use of hexobarbitone is pronation of the arm during injection and muscle tremors, and these undoubtedly appear and complicate the issue at first, but as experience is gained they appear less and less often until they are experienced so rarely as to be discounted altogether.

Despite what Dr. Leatherdale *et al.* say, I make no claim for "brevidil" (suxamethonium bromide), I merely postulated that the reason why I so seldom encounter muscle pains is that I use a freshly prepared solution, and since then I have been using a "kept" solution with no appreciable difference. I do not, however, make my solution with normal saline. I wish an answer were arrived at, but in the meanwhile I am not inclined to abandon a drug which I find so satisfactory, and I shall endeavour to find the absolute incidence amongst my patients.—I am, etc.,

Alberta, Canada. J. SHEGOG RUDDELL.

Sphygmomanometry and Arm Circumference

SIR,—Dr. Stanley Higham has recently suggested (*Journal*, April 4, p. 906) that errors occurring in the measurement of blood pressure due to arm circumference might conveniently be allowed for by using a suitably calibrated hook-type armlet. The corrections which would have to be applied are of doubtful importance, except perhaps for group studies, and even then may not be applicable to this type of cuff. Comparisons between intra-arterial pressures and pressures recorded indirectly using a sphygmomanometer and the clip-on type of cuff have not, to my knowledge, been made. However, the results of surveys in which this type of cuff[1] was used suggested that the recorded blood pressure was not affected by the size of the arm.

It would be wise to await further evidence on this matter before marking these armlets with "corrections" which may be spurious.—I am, etc.,

Sydney Hospital, Sydney, Australia. H. M. WHYTE.

REFERENCE

[1] Whyte, H. M., *Circulation*, 1959, **19**, 511.

Top Executives

SIR,—I have read with considerable interest the joint letter of Dr. Arthur Levin and Mr. H. Beric Wright (*Journal*, June 13, p. 1531) regarding the examination of top executives. Some three years ago I introduced into the industrial concern of which I am the medical officer an annual medical check of such individuals, and have been impressed with the results. I think that those that condemn this procedure as useless have neither experience nor knowledge of its application in practice.

I would, however, stress that in my view the most important aspect of this routine is the promotion and maintenance of health rather than its value in early diagnosis. While undoubtedly a regular examination will pick up such conditions as asymptomatic albuminuria, glycosuria, hypertension, early peptic ulceration, and pulmonary lesions, the greater value, I feel, lies in the opportunity it presents for preventive medicine and health education. Few doctors have time and opportunity for regular discussions with their symptomless patients, and it is surprising what a need there is for the most simple and obvious advice. These executives are responsible individuals, and I find most receptive to advice. One has little difficulty in developing the same prudence, without hypochondriasis, with regard to their health as they already possess in their attitude to the machinery which they manage, which undergoes regular maintenance and overhaul.

To give specific examples. It is part of my procedure to see that there are regular periodic eye and dental checks—normally a great deal of slackness is found in this direction; to ensure a good balanced diet—it is surprising how many have an inadequate intake of fresh fruit or vegetables; of increasingly recognized importance, to bring about weight reduction—in the course of three years I have succeeded in getting 75% of those who were overweight down to their correct levels; to encourage the taking of regular exercise with adequate fresh air and suitable relaxations; sufficient holidays and seeing that these are taken away from home; to discourage and in some cases stop smoking; and finally to recommend to management where indicated a period of rest in any individual where tension is mounting, and thus prevent by timely intervention a more prolonged absence due to physical or mental breakdown. I give this type of advice and I find it is taken. The individual feels better and keeps fitter, and, to me, this is a gratifying result and one that is clearly economically sound, as all intelligent managements will recognize.—I am, etc.,

London, W 13. E. C. LIVINGSTON.

Crackpot

Mr. W. S. HODGES (London, W.2) writes: In the review of a dictionary of psychology by Horace B. English and Ava Champney English (*Journal*, March 28, p. 836), reference was made to the use of the word "psychoceramic." Should we not consider schizoceramic as being more appropriate for a "crackpot"?

Physiotherapy in Arthritis

Dr. THOS. LOGAN (Hemyock, Devon) writes: We have been closing our eyes to the uselessness of certain therapeutic procedures for too long. There must be many experienced doctors who have been forced to arrive at conclusions similar to those of Miss D. E. Hamilton, Professor E. G. L. Bywaters, and Mr. N. W. Please (*Journal*, February 28, p. 542). The Hinchliffe Committee has suggested that doctors whose prescribing costs are 50% over the average should be fined heavily, and doubtless in this category are many practitioners who by judicious use of costly drugs are keeping patients out of hospital and at work, with a consequent saving. The waste that occurs as a result of loose prescribing is, in my opinion, negligible compared with the money spent on futile physiotherapy applied to patients transported to and from the department in expensive hospital cars.

Obituary

GRANTLY DICK-READ, M.D.

Dr. Grantly Dick-Read, who died in Norfolk on June 11, aged 69, was well known in Britain and many countries overseas for his pertinacious and enthusiastic advocacy of "natural childbirth." His views, and the ways he expressed them, gave rise to controversy, but the soundness of many of the principles on which he based his teaching was not in question.

Grantly Dick Read (he changed his name to Dick-Read last year) was born on January 26, 1890, the son of a Norfolk miller and the sixth of seven children. He was educated at Bishop's Stortford College and St. John's College, Cambridge. A keen athlete, boxer, and games player, he played association football for the university on occasions and was a member of the Hawks Club and of the Incogniti and Cryptics cricket clubs. Going on to the London Hospital for his clinical training, he graduated B.Ch. in 1914 and joined the R.A.M.C. very shortly afterwards on the outbreak of the first world war. He served first in Gallipoli, where he was wounded, and later in France, first as medical officer to the 5th Dragoon Guards and later as D.A.D.M.S. to the Indian Cavalry Corps. At the end of the war he returned to the London Hospital as resident accoucheur, and in 1920 he proceeded to the M.D. of Cambridge University.

After a short spell in general practice in Eastbourne he went into a partnership in Woking, where he remained for many years. There he was able to develop his special interest in obstetrics and to work out his views on childbirth. His reputation grew and he took rooms in Harley Street. The general-practice partnership in Woking was dissolved in 1934, and after that he practised obstetrics independently, working in his own private clinic in Woking. At this time he began to write extensively on "natural childbirth" and to give lectures on the subject. Later, after the second world war, he undertook a lecture tour in the U.S.A. and he also lectured in Paris. Finding he could not practise in England to his satisfaction after the Health Service came into being in 1948, he went out to South Africa, and after a struggle with the South African Medical and Dental Council and surmounting other difficulties he established a practice in Johannesburg. He returned to live in England in 1953, but by then he had given up active practice and devoted his time to lecturing and writing.

Dr. Dick-Read was twice married. He first married Dorothea Cannon in 1921 and they had two sons and two daughters. In 1952 he married Mrs. Jessica Bennett.

A colleague writes: Grantly Dick-Read evolved his theory of natural childbirth as a result of careful study of the process of childbirth. According to him the event which led to the development of his theories took place in Whitechapel in 1914. There he tried to give chloroform to a woman in labour. She refused, gently but firmly, and when it was over she remarked, "It didn't hurt, doctor. It wasn't meant to hurt, was it?" During the years which followed this question must have been in his mind. His first important publication was *Natural Childbirth* (1933). Here he stated his belief that normal childbirth should be a painless process and that pain arises from fear and tension. If these were abolished, he maintained, the pain of labour could be largely eliminated. Much of his early work was based on Jacobson's book on relaxation published in 1929. As a result of this a planned method of natural childbirth was evolved based partly on the practice of muscular relaxation and partly on antenatal exercises.

Natural Childbirth was followed by other books: *Revelation of Childbirth* (1943), *Childbirth Without Fear* (1944), *Birth of a Child* (1947), *Introduction to Motherhood* (1950), and *No Time for Fear* (1955). Among the articles he published in medical journals was one in this *Journal*—the substance of a lecture he gave in 1949 on "The Discomforts of Childbirth." He also made a film to illustrate his method of conducting labour, and he was well known as a broadcaster.

His work was taken up by many in Britain, and he received the support of some leading obstetricians. The late Helen Heardman, a physiotherapist, was greatly attracted by Dick-Read's views, and she was instrumental in starting classes for expectant mothers in many centres. Dick-Read's methods have also been practised, with modifications, in many countries, notably by H. Thoms at the Yale University clinic in the U.S.A. The Russians have evolved a "psychoprophylactic" method, also practised in France, which has some differences from that originally described by Dick-Read but which resembles it in many respects. The extent of his achievement is thus to be seen all over the world, for his work has had a great popular appeal.

He himself often felt that his work was not appreciated by his medical colleagues and that his own profession was slow to recognize his contribution. Certainly at the time of his first publications there was much room for improvement of the maternity services, in the conduct of labour, and in the attitude of obstetricians and midwives to the act of childbirth. His ideas were a complete reaction against "twilight sleep" and the excessive practice of operative delivery. He encouraged the mother to enjoy her delivery in complete consciousness of the event. On the other hand, many of his views were misunderstood and misinterpreted. He was not against analgesia in obstetrics, and indeed often said that analgesia should always be available and offered where needed. But he contended that a confident and adequately prepared woman experiencing a normal birth should need only minimal relief.

Grantly Dick-Read was a man of striking appearance and handsome presence. He was a brilliant speaker, expounding his views with single-minded enthusiasm which carried his audience with him. In private life he was very gay and excellent company, and he enjoyed the good things of life. His contribution to the art of obstetrics was a unique one—one which could probably have been made by no one else and made only by one who was prepared to rebel against the established order. We extend to his widow and family our sympathy at the passing of one who devoted his life to a single cause, but one of the highest importance.

DEATHS

Anderson.—On May 31, 1959, at The Beild, Kinross, Hope Pitcairn Anderson, M.B., Ch.B.

Anderson.—On May 30, 1959, William Anderson, *M.C.*, M.B., Ch.B., of "Rocklands," Whaley Bridge, Derbyshire, formerly of Manchester.

Aschkanasy.—On May 27, 1959, at Worthing, Sussex, Willy Aschkanasy, M.D., aged 81.

Bellsham-Revell.—On May 30, 1959, Lawrence Cecil Bellsham-Revell, M.B.E., M.R.C.S., L.R.C.P., L.D.S., of 14, High View Road, Sidcup, Kent, aged 46.

Dunkley.—On May 22, 1959, Edward Vincent Dunkley, M.D., of Hatcham House, Hawkhurst, Kent, aged 80.

Evans.—On June 8, 1959, at the West Wales General Hospital, Carmarthen, Alan Meredith Evans, M.R.C.S., L.R.C.P., of Awelon, Llandyssul, Cards.

Fyfe.—On June 2, 1959, at his home, Kintore, Cupar, Fife, George Matthew Fyfe, C.B.E., M.B., F.R.C.P.Ed., D.P.H.

Gasking.—On May 20, 1959, at Beldornie, Ryde, Isle of Wight, Cyril Trist Gasking, M.D.

Hamilton.—On May 29, 1959, at his home, The Old Vicarage, Exhall, Coventry, Warwickshire, William Joseph Hamilton, M.D.

Hughes.—On May 30, 1959, George Sidney Norman Hughes, D.S.O., L.M.S.S.A., Colonel, late R.A.M.C., retired, of Birchgrove, Trawscoed, Cards, aged 51.

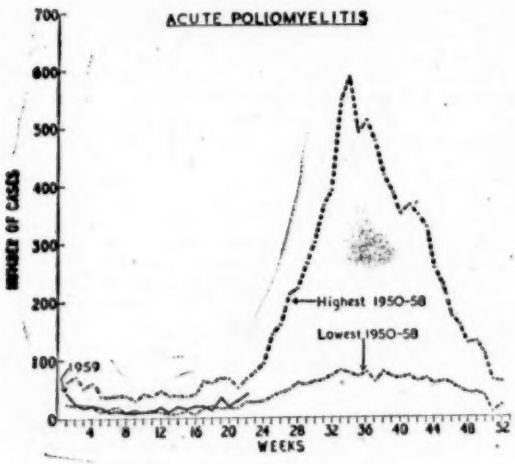
Macfadyen.—On June 5, 1959, at the Lister Hospital, Hitchin, Herts, Norman Macfadyen, M.B., D.P.H., of Letchworth, Herts, aged 82.

MacLennan.—On May 22, 1959, at Victoria Infirmary Annexe, Glasgow, William Alexander MacLennan, M.B., Ch.B., of 25, Boclair Road, Hillfoot, Glasgow.

Macnab.—On June 4, 1959, in a nursing-home, Eastbourne, Sussex, John Theodore Macnab, M.B., B.Ch., D.P.H., of 59, King's Drive, Eastbourne, aged 79.

Malik.—On June 5, 1959, Khivroun Malik, M.R.C.S., L.R.C.P., L.D.S., of London, N.

McCann.—On June 1, 1959, at 15, Carr Lane, Shipley, Yorkshire, Francis James McCann, M.B., B.Ch.



Week Ending June 6

Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available

	Week Ending May 30	Week Ending June 6
Measles		
Cumberland	170	211
Carlisle C.B.	53	107
Essex	608	632
Harlow U.D.	63	142
Kent	427	621
Orpington U.D.	13	131
Dysentery		
Durham	17	23
South Shields C.B.	8	10
Hampshire	9	20
Southampton C.B.	7	20
Lancashire	165	165
Darwen M.B.	6	13
Heywood M.B.	11	23
London	83	88
Hackney	1	10
Lewisham	15	14
Middlesex	44	55
Edmonton M.B.	16	22
Northamptonshire	20	16
Daventry M.B.	20	15
Staffordshire	32	41
Stoke-on-Trent C.B.	10	12
Sussex	22	25
Brighton C.B.	14	18
Yorkshire East Riding	64	57
Kingston upon Hull C.B.	36	49
Yorkshire West Riding	87	96
Bradford C.B.	22	25
Leeds C.B.	40	46
Monmouthshire	17	35
Ebbw Vale U.D.	13	25
Glasgow	140	111
Acute Poliomyelitis		
London	10	14
Islington	8	8
Food-poisoning		
Yorkshire East Riding	32	44
Derwent R.D.	29	44

Medical News

Royal College of Surgeons of England. — At an extraordinary meeting of the Council on June 10 Dr. PAUL R. HAWLEY, director of the American College of Surgeons, was admitted to the Honorary Fellowship of the College, after a citation had been made in his honour by Professor DIGBY CHAMBERLAIN. Dr. A. H. BENNETT, Dr. S. F. L. DAHNE, Sir JOSEPH H. PIERRE, and Professor A. J. E. CAVE were formally admitted to the Fellowship. Dr. R. H. P. FITZPATRICK and Dr. G. A. HAYDOCK were formally admitted to the Fellowship in the Faculty of Anaesthetists.

At an ordinary meeting on June 11 the Lady Cade Medal was presented to Squadron-Leader T. C. D. WHITESIDE and the Hallett Prize to Dr. D. F. WEINMAN, of Ceylon. The following were co-opted to the Council for the year 1958-9.—*General Practice*: Dr. JOHN H. HUNT; *Anaesthetics*: Dr. G. S. W. ORGANE; *Ophthalmology*: Mr. T. KEITH LYLE; *Gynaecology and Obstetrics*: Mr. A. C. H. BELL; *Radiology*: Professor D. W. SMITHERS; *Otolaryngology*: Mr. C. GILL-CAREY; and *Dental Surgery*: Sir WILFRID FISH. The following were elected to the Fellowship in the Faculty of Dental Surgery: Mr. W. E. EARLE (U.K.), Dr. DON GULLETT (Canada), Professor K. SUTHERLAND (Australia), and Dr. P. H. JESERICH (U.S.A.). A diploma of membership was granted to E. M. BLENKINSOPP, of St. Mary's Hospital. The award of the Gilbert Blane Medal for 1959 to Surgeon Commander J. GLASS was approved.

U.S.A. Cancer Fellowship.—The Memorial Center for Cancer and Allied Diseases, which is affiliated with Cornell Medical School, is offering a Fellowship in Medical Neoplasia to be held at the Center in New York from July 1, 1960. The stipend is to be $6,000 a year without maintenance, and the appointment is normally for one year only, though it may be renewed. Candidates must be graduates of medical schools recognized by the American Medical Association. Details from Dr. H. D. DIAMOND, at the Center, 444, East 68th Street, New York, 21, New York.

Marie Curie Memorial Foundation.—The work of the Foundation, which was established in 1948, includes extensive welfare activities for those suffering from cancer. Seven residential homes for cancer patients have already been established in the United Kingdom, and further homes will be provided as soon as possible. The Foundation also operates an area welfare grant scheme to help those cancer patients who are being nursed at home. Details from the Secretary of the Foundation, Education and Welfare Sub-committee, 124, Sloane Street, London, S.W.1.

National Corporation for the Care of Old People.—The Corporation is to finance a two-year programme of research in geriatric nursing at the Whittington Hospital, London, under the direction of Dr. A. N. EXTON-SMITH, physician in charge of the geriatric unit. The research team, which hopes to start work in July, will investigate geriatric nursing problems with a view to improving nursing methods, and will seek ways and means of helping elderly patients to become more self-reliant. It will also try to determine which kinds of nursing equipment and invalid furniture are most suitable for use in old people's wards and homes.

Mental Illness Research Donation.—The Mental Health Research Fund has received a donation in unusual circumstances. The late Mr. A. J. DAVIES, who was killed recently in an air crash, left no will, but amongst his papers was a note saying that, in the event of his death, he wished £15,000 to be paid from his estate to the Mental Health Research Fund. Mr. Davies's next-of-kin decided to give effect to the wish, and the gift, to be known as "The Arnold Davies Fund," will be applied to the study of mental illness.

Pharmaceutical Society.—On June 12, the hundredth anniversary of the death of Jacob Bell, who founded the

Pharmaceutical Society in 1841, the president of the Society, Mr. GWILYM HUGHES, unveiled a tablet to Bell's memory in Woodbury Park Cemetery, Tunbridge Wells, where he is buried. In the evening Mr. Hughes gave a review of Jacob Bell's life and work at the Society's House in Bloomsbury Square, where a commemorative exhibition was also held.

American Goiter Association Prize.—The Van Meter Prize Award of $300 is offered for the best unpublished essay on "Goiter—especially its basic cause," to be presented at the Fourth International Goitre Conference in London in July, 1960. Closing date January 1, 1960. Details from Dr. JOHN C. MCCLINTOCK of the association, 149½, Washington Avenue, Albany, 10, New York.

Empire Rheumatism Council.—The Council has made a grant of £6,000 (£2,000 a year for three years) for research that is being carried out in New Zealand under Professor Sir HORACE SMIRK at Otago University, Dunedin. The grant may be extended to five years, after which it is hoped that it will continue with funds raised in New Zealand.

Medical Photography.—The Royal Photographic Society's Hood Medal for 1959 has been awarded to Mr. VICTOR WILLMOTT, F.I.B.P., F.R.P.S., for "his outstanding photographic work, particularly in the field of medical photography." The combined colleges' bronze medal given by the Royal College of Surgeons, the Royal College of Physicians, and the Royal College of Obstetricians and Gynaecologists has been awarded to Mr. RAYMOND LUNNON, A.R.P.S., A.I.B.P., for his work on direct ultra-violet photography in dermatology.

Tetanus in Cotton-wool.—Owing to the danger of tetanus hospitals are warned against using unbleached cotton-wool in a memorandum from the Ministry of Health (H.M. (59) 53). Bleached cotton-wool has also been found to contain tetanus spores. Consequently, only when it is satisfactorily sterilized is it entirely safe to use in wound dressings.

Gairdner Foundation.—Professor W. D. M. PATON, F.R.S., professor of pharmacology at the Royal College of Surgeons, and Professor ELEANOR ZAIMIS, professor of pharmacology at the Royal Free Hospital School of Medicine, have been jointly awarded $5,000 by the Foundation for their discovery in 1948 of the hexamethonium compounds.

Royal Society of Medicine.—At a general meeting of Fellows of the Society, Professor CLARENCE CRAFOORD (Sweden), Sir HAROLD GILLIES, Sir CHARLES HARINGTON, F.R.S., Sir ARTHUR MACNALTY, and Sir RUDOLPH PETERS, F.R.S., were elected to honorary Fellowship.

Kuru.—An exhibition on this disease is now on display at the Wellcome Museum of Medical Science, and will remain there till the end of August. Kuru is the acute degenerative neurological disorder recently found among the Fore natives of New Guinea (see *Journal*, December 21, 1957, p. 1480).

Hospital Bank.—The first full-time bank branch to be run inside a Scottish hospital was officially opened at Edinburgh Royal Infirmary earlier this month by Professor G. J. ROMANES, chairman of the hospital's management board.

Claim to Peerage.—After seven years' research, Brigadier F. D. ANNESLEY, of Nailsworth, Gloucestershire, has established his claim to the title of Viscount Valentia in the Irish peerage, which has been considered dormant since 1844. Lord Valentia retired from the Royal Army Medical Corps in 1948.

Register of Operating Theatre Technicians.—The fourth edition of the Register has now been published by the Board of Registration of Medical Auxiliaries. Copies are supplied free to registered medical practitioners and employing authorities (others 5s., post free), on application to the Registrar of the Board, B.M.A. House, Tavistock Square, London, W.C.1.

Medical Benevolent Fund.—The Fund's new address is 37, George's Road, Wimbledon, London, S.W.19. (WIM 1792).

Professor B. F. Maegraith, dean of the Liverpool School of Tropical Medicine, has been appointed honorary civil consultant in tropical hygiene to the Royal Air Force.

Dr. D. P. Cuthbertson, director of the Rowett Research Institute, has been invited to give the third Baxter Lecture on September 29 to the American College of Surgeons.

University of Wales.—Sir HAROLD HIMSWORTH, F.R.S., secretary of the Medical Research Council, is to receive an honorary LL.D. in Aberystwyth on July 15

COMING EVENTS

"Radiation and Ageing."—Third (annual) Ciba Foundation Lecture on Research on Ageing: Dr. A. C. UPTON, July 2, 2.30 p.m. Tickets from Assistant Secretary, The Ciba Foundation, 41, Portland Place, London, W.1.

European Organization to Co-ordinate Research on Fluoridation and the Prevention of Dental Caries.—Pavia, Italy, July 2–5. Details from Professor Dr. SILVIO PALAZZI, Clinica Odontoiatrica dell'Universita, Pavia, Italy.

Cambridge Graduates' Medical Club.—Annual general meeting and dinner will be held at Trinity Hall on July 3. Will members who have not yet received notification, or other Cambridge men who are interested, write to Mr. H. H. E. BATTEN, 69, Bridge Street, Cambridge.

The Nutrition Society.—Symposium on "Nutrition and Reproduction": School of Veterinary Medicine, Madingley Road, Cambridge, July 4, 10.30 a.m. Details from Miss D. F. HOLLINGSWORTH, c/o Ministry of Agriculture, Fisheries, and Food, Great Westminster House, Horseferry Road, London, S.W.1.

Third International Congress of School and University Health.—Paris, July 6–8. Further details from Comité d'Organisation du Congrès d'Hygiène Scolaire et Universitaire, 13, rue du Four, Paris, 6.

Royal Society of Health.—Symposium on "The Maintenance of Family Life in Relation to Children under 5 in the Present-day Social Structure," July 8, 2.30 p.m., 90, Buckingham Palace Road, London, S.W.1.

Imperial Cancer Research Fund Concerts.—July 12, 8.30 p.m., The George, Colchester: Denis Matthews.

NEW ISSUES

SPECIALIST JOURNALS AND ABSTRACTS

The journals listed below are available from the Publishing Manager, B.M.A. House, Tavistock Square, London, W.C.1.

British Heart Journal.—Issued quarterly (£3 annually). The new issue (Vol. 21, No. 2) includes:

THE ANOMALOUS ORIGIN OF THE LEFT CORONARY ARTERY FROM THE PULMONARY ARTERY. John D. Keith.
THE RADIOLOGICAL FEATURES OF SYPHILITIC AORTIC INCOMPETENCE. W. G. Smith and J. C. Leonard.
ENDOMYOCARDIAL FIBROSIS IN THE CEYLONESE. N. Nagaratnam and R. V. P. Dissanayake.
MITRAL RESTENOSIS. G. C. Patterson and J. R. Marshall.
FURTHER OBSERVATIONS ON COUPLED EXTRASYSTOLES AND AUTOMATIC VENTRICULAR RHYTHMS. A. Schott and D. Scherf.
PULMONARY VASCULAR CHANGES IN A DOG AFTER AORTO-PULMONARY ANASTOMOSIS FOR FOUR YEARS. Donald Heath, David E. Donald and Jesse E. Edwards.
THE LESS COMMON FORMS OF PULMONARY HYPERTENSION. William Evans.
HEART FAILURE IN PATIENTS WITH HIGH BLOOD PRESSURE. J. N. Mackerson.
SPONTANEOUS CAPILLARY PULSATION IN COMPLETE HEART BLOCK. G. A. MacGregor.
ENDOCARDIAL FIBRO-ELASTOSIS IN ADOLESCENTS AND ADULTS. P. N. P. van Buchem, A. Arends and E. A. Schröder.
THE HEART LUNG COEFFICIENT IN OLDER PEOPLE. Nairn R. Cowan.
DEVELOPMENT OF VALVULAR LESIONS IN METASTATIC CARCINOID DISEASE. Åke Thorson and Olof Nordenfelt.
AMISOMETRADINE (ROLICTON) IN THE TREATMENT OF CONGESTIVE HEART FAILURE. Margaret M. Platts.
STUDIES IN PULMONARY HYPERTENSION IN CONGENITAL HEART DISEASE. Howard B. Burchell.
UNEXPLAINED ELECTROCARDIOGRAMS IN THE AFRICAN. S. J. Powell.
HUNTER'S POLYDYSTROPHY (GARGOYLISM) WITH CARDIAC LESIONS AND SOME FORMES FRUSTES. R. E. Steed.
EFFECT OF DOMYNOLIC ACID ON EXPERIMENTAL ATHEROMA IN THE COCKEREL. R. S. F. Campbell, T. D. V. Lawrie, J. C. MacLaurin, and R. Pirrie.
ASPECTS OF PULMONARY BLOOD FLOW IN ATRIAL SEPTAL DEFECT. Lawson McDonald, Richard Emanuel, and Malcolm Towers.
JAMES WILLIAM BROWN.
CASE REPORT:
EFFORT SYNCOPE IN AORTIC STENOSIS. David Leak.